

Task History

June 22, 2011 10:39 PM

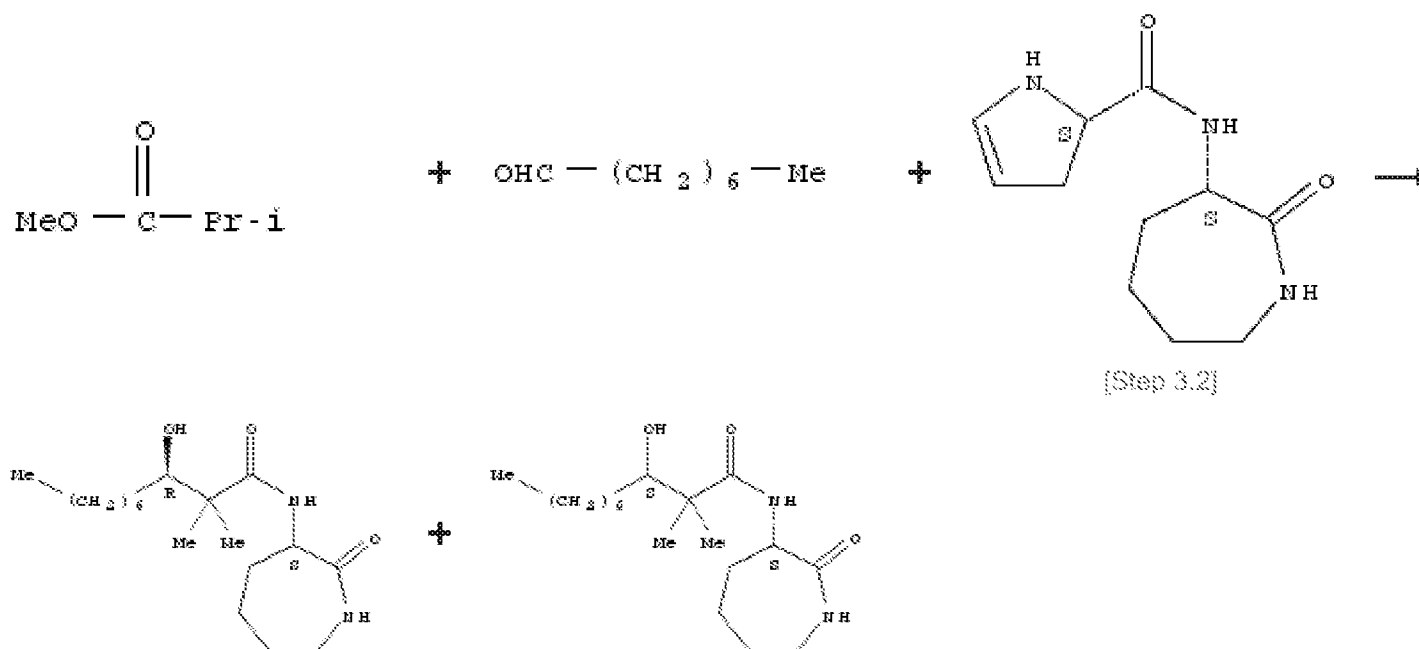
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Answer set 9 created with 1 reference answer from CAPLUS

Retrieve reaction information in 1 reference of Answer set 9

Answer set 10 created with 76 reactions

1. 3 Steps



Overview

Steps/Stages

- 1.1 R:LiN(Pr-i)₂, S:THF, 45 min, -78°C
- 1.2 18 h, -78°C → rt
- 1.3 R:NH₄Cl, S:H₂O, rt
- 2.1 R:KOH, S:H₂O, S:EtOH, 18 h, reflux; cooled
- 2.2 S:H₂O, pH 2
- 3.1 R:1-Benzotriazolol, R:EtN=C=N(CH₂)₃NMe₂•HCl, S:THF, 4 h, rt
- 3.2 R:Disodiumcarbonate, S:H₂O, 18 h, rt

Notes

1) reaction from p.46 in patent, 2) Na₂SO₄/NaHSO₄ buffer used in stage 2, reaction from p.46 in patent, 3) stereoselective, combined yield = 88%, reaction from p.47 in patent, Reactants: 3, Reagents: 6, Solvents: 3, Steps: 3, Stages: 7, Most stages in any one step: 3

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Step 1

Example 57; Methyl 2,2-dimethyl-3-hydroxy decanoate (Intermediate), Butyllithium (2.5 M in hexanes, 50 mmol) was added to a solution of diisopropylamine (50 mmol) in dry THF (200 ml) at -78 °C under an atmosphere of dry nitrogen. The reaction was stirred for 30 minutes, and then methyl isobutyrate (50 mmol) was added. After 45 minutes, decanal (50 mmol) was added and the reaction was allowed to warm to ambient temperature over 18 hours. After the addition of saturated aqueous ammonium chloride (10 ml), the reaction solvent was removed in vacua and the residue was partitioned between hexanes and pH 2 buffer (0.5 M Na₂SO₄ / 0.5 M NaHSO₄). The organic layer was dried over Na₂SO₄ and the solvent was removed to give methyl 2,2- dimethyl-3-hydroxy decanoate as an oil (9.98g, 77%). Methyl 2,2-dimethyl-3-hydroxy decanoate (Intermediate), Yield (9.98g, 77%). δH (400 MHz, CDCl₃) 3.70 (3H, s, OCH₃), 3.69 (1H, dd, J10, 2, CHOH), 1.68-1.20 (16H, m, (CH₂)₈), 1.19 (3H, s, CCH₃), 1.17 (3H, s, CCH₃) and 0.88 (3H, t, J 7 , CH₂CH₃) (no OH observed).

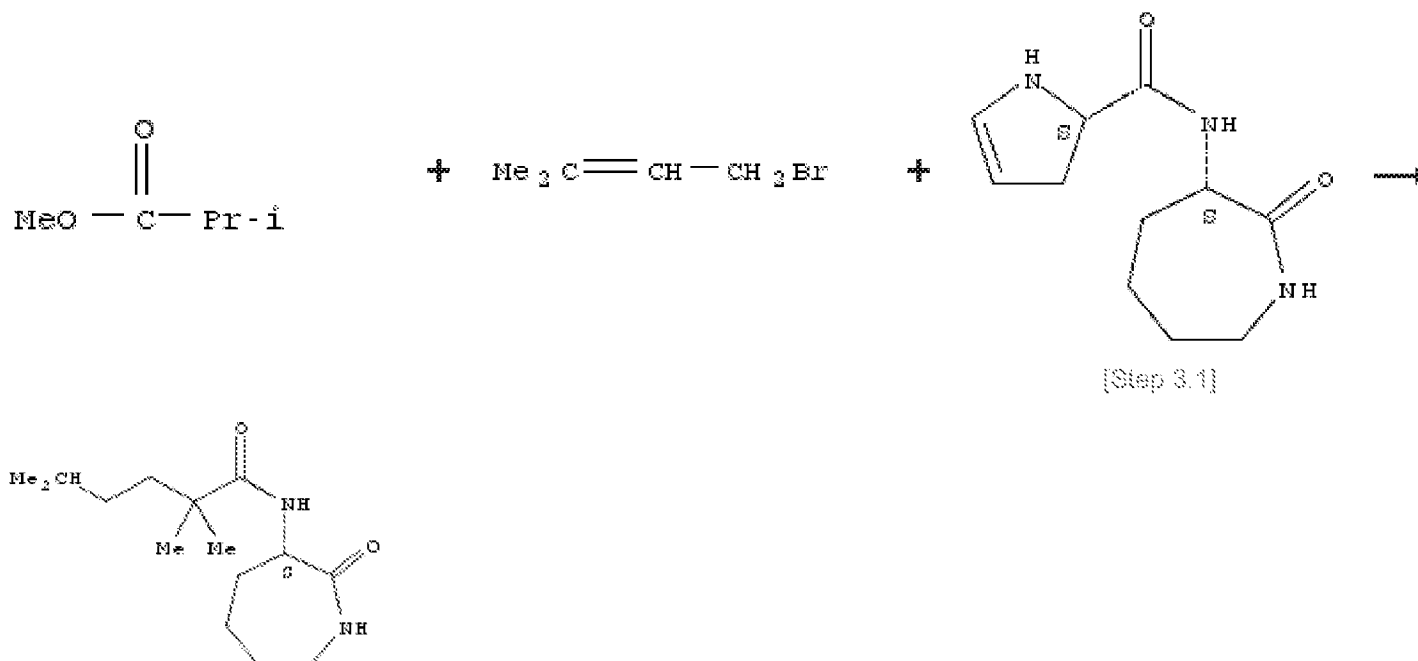
Step 2

Example 58: 2,2-Dimethyl-3-hydroxy decanoic acid (Intermediate). Methyl 2,2-dimethyl-3-hydroxy decanoate (20 mmol) was dissolved in EtOH (80 ml) and a solution of KOH (40 mmol) in water (20 ml) was added. The reaction was heated at reflux for 18 hours, and then the reaction was allowed to cool. The solvent was removed in vacuo and the residue was partitioned between water and diethyl ether. The aqueous layer was then acidified with pH 2 buffer (0.5 M Na₂SO₄ / 0.5 M NaHSO₄ and extracted with diethyl ether. The solution was dried over Na₂SO₄ and rediced in vacuo to give 2,2-dimethyl-3-hydroxy decanoic acid which solidified on standing 2,2-Dimethyl-3-hydroxy decanoic acid (Intermediate) m.p. 39-41 °C; δ H (400 MHz, CDCl₃) 3.64 (1H, dd, J10, 2, CHOH), 1.67-1.12 (22H, m, (CH₂)₈ + C(CH₃)₂) and 0.88 (3H, t, J7, CH₂CH₃).

Step 3

Example 59(a): (3S,3'R) and Example 59(b): (3S,3'S)-3-(3'-Hydroxy-2',2'-dimethyldecanoyl)aminocaprolactam: 2,2-Dimethyl-3-hydroxy decanoic acid (1.77 mmol) and 1-hydroxybenzotriazole monohydrate (1.77 mmol) were dissolved in THF (10 ml). 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.77 mmol) was added and the reaction was stirred at ambient temperature for 4 hours. A solution of (S,S)-3- amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (2 mmol) and Na₂CO₃ (6 mmol) in water (15 ml) was added and the reaction was stirred for 18 hours. The reaction solvent was then removed in vacua and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with pH 2 buffer (0.5 M Na₂SO₄ / 0.5 M NaHSO₄ and dilute aqueous sodium hydroxide, and then dried over Na₂SO₄ and reduced in vacua. The residue was chromatographed on silica gel (25% ethyl acetate in hexanes to 100% ethyl acetate) to give a mixture of (3S,3R) and (3S,3'S)-3-(3'-hydroxy-2',2'-dimethyldecanoyl)amino-caprolactams (557 mg, 88%). Example 59(a): (3S,3'R) and Example 59(b): (3S,3'S)-3-(3'-Hydroxy-2',2'-dimethyldecanoyl)aminocaprolactam, Yield (557 mg, 88%). δ H (500 MHz, CDCl₃) 7.28 (1H, d, J 6, NHCH one isomer), 7.25 (1H, d, J6, NHCH, one isomer), 6.62-6.48 (1H, br m, NHCH₂, both isomers), 4.53-4.42 (1H, m, NCH, both isomers), 3.77 (1H, br d, J, 6, OH, one isomer), 3.63 (1H, br d, J, 6, OH, one isomer), 3.47-3.36 (1H, m, CHOH, both isomers), 3.32-3.17 (2H, m, NCH₂, both isomers), 2.07-1.92 (2H, m, lactam CH x2, both isomers), 1.87-1.71 (2H, m, lactam CH x2, both isomers), 1.60- 1.17 (21H, m, lactam CH x2 + chain (CH₂)₈ + CH₃, both isomers), 1.14 (3H, s, CCH₃, both isomers) and 0.84 (3H, t, J 7, CH₂CH₃, both isomers); δ c (125 MHz, CDCl₃) 177.6, 177.2, 175.8 (CO, both isomers), 77.8, 77.4 (CHOH), 52.1 (NCH, both isomers), 45.9, 45.8 (C(CH₃)₂), 42.1, 42.0 (NCH₂), 31.9 (x2) 31.6, 31.3, 30.9, 29.6 (x4), 29.3, 28.8, 27.9, 26.7, 26.6, 22.6 (CH₂), 23.7, 23.5, 21.1, 20.4 and 14.1 (CH₃).

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2. 4 Steps

Overview

Steps/Stages

- 1.1 R:LiN(Pr-i)₂, S:THF, 1 h, -78°C
- 1.2 14 h, -78°C → rt
- 2.1 R:NaOH, S:H₂O, S:EtOH, 6 h, reflux; cooled
- 2.2 R:Cl(O=)CC(=O)Cl, C:DMF, S:CH₂Cl₂, 1 h
- 3.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 12 h, rt
- 4.1 R:H₂, C:Pd(OH)₂, S:AcOEt, 14 h, rt

Notes

1) reaction from p.37 in patent, 2) reaction from p.38 in patent, 3) reaction from p.30 in patent, 4) reaction from p.30 in patent, Reactants: 3, Reagents: 5, Catalysts: 2, Solvents: 5, Steps: 4, Stages: 6, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 18 Jun 2005

Experimental Procedure

Step 1

Methyl 2,2,5-trimethyl-hex-4-enoate: butyllithium (2.9 M, 50 mmol) was added to a solution of diisopropylamine (7.2 ml, 50 mmol) in dry THF (200 ml) at -78 °C under N₂. The reaction was stirred at -78 °C for 20 minutes and then methyl isobutyrate (5.7 ml, 50 mmol) was added. The reaction was stirred at -78 °C for 1 hour, and then 3-methyl-but-2-enyl bromide (5.8 ml, 50 mmol) was added and the reaction was allowed to warm to ambient temperature over 14 hours. The reaction solvent was then removed in vacuo, and the residue was partitioned between pH 2 aqueous buffer (0.5 M NaHSO₄ / 0.5 M Na₂SO₄) and hexane (3 x 250 ml). The combined organic layers were dried over Na₂SO₄ and the hexane solvent removed in vacuo to give methyl 2,2,5-trimethyl-hex-4-enoate as a colourless oil (6.93 g 81%). Methyl 2,2,5-trimethyl-hex-4-enoate, Yield (6.93 g 81%). $\nu_{\max}/\text{cm}^{-1}$ 1732 (CO); δ_{H} (400 MHz, CDCl₃) 5.04 (1H, tsept, J7.5, 1.5, CH=C), 3.63 (3H, s, OCH₃), 2.20 (2H, d, J7.5, CHCH₂), 1.68 (3H, br s, CH=CMeMe), 1.58 (3H, br s, CH=CMeMe), 1.14 (6H, s, (CH₃)₂CO); δ_{C} (125 MHz, CDCl₃) 178.4 (CO), 134.1 (Me₂OCH), 119.8 (Me₂C=CH), 51.6 (OCH₃), 42.8 (Me₂CCO), 38.7 (CH₂), 25.9, 24.7 (x 2), 17.8 (CCH₃); m/z (MH⁺ C₁₀H₁₉O₂ requires 171.1385) 171.1388.

Step 2

2,2,5-Trmiethyl-hex-4-enoyl chloride: methyl 2,2,5-trimethyl-hex-4-enoate (2.74 g, 16 mmol) was dissolved in ethanol (50 ml) and added to a solution of NaOH (3.0 g, 75 mmol) in water (35 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacua*. The residue was partitioned between pH 2 aqueous buffer (0.5 M NaHSO₄ / 0.5 M Na₂SO₄) and diethyl ether (3x150 ml). The combined organic layers were dried over Na₂CO₃ and the ether solvent removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoic acid (>95% pure) as a colourless oil. The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoyl chloride which was all used without purification in the next step. **2,2,5-Trmiethyl-hex-4-enoyl chloride.**

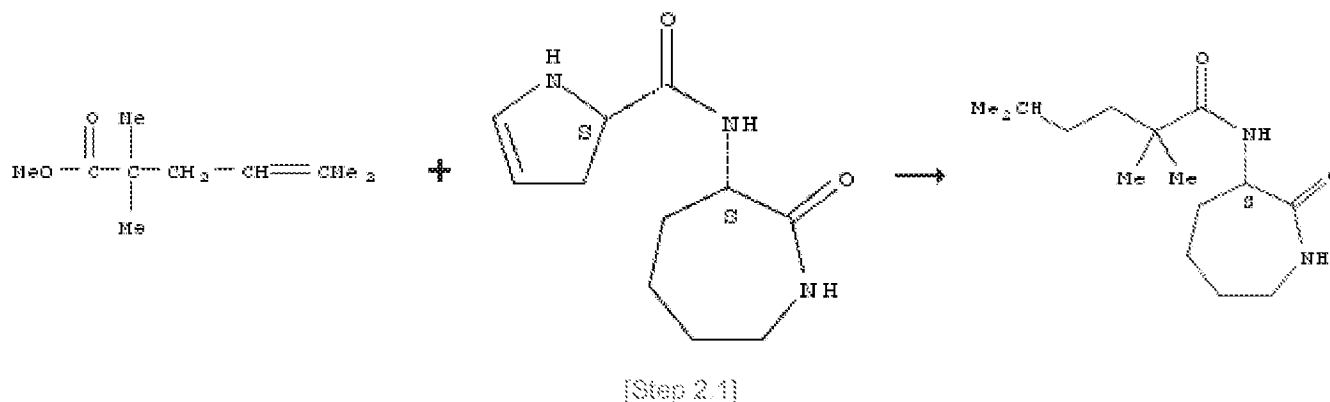
Step 3

Example 23: (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactamhydro-pyrrolidine-5-carboxylate (4.11 g, 16 mmol) and Na₂CO₃ (5.09 g, 48 mmol) in water (50 ml) were added to a solution of 2,2,5-trimethyl-hex-4-enoyl chloride (16 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 50 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacua. The residue was purified by silica column chromatography (1:5 EtOAc: hexanes to EtOAc) to give (S)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam as a waxy solid (3.58 g, 84%). (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam, Yield (3.58 g, 84%). m.p. 43-44 °C; $[\alpha]_{\text{D}}^{25}$ (c = 1, CHCl₃) +23.2; $\nu_{\max}/\text{cm}^{-1}$ 3394, 3251 (NH), 1674, 1633 (CO), 1503 (NH); δ_{H} (500 MHz, CDCl₃) 7.11 (1H, d, J5.0, CHNH), 6.65-6.45 (1H, br m, CH₂NH), 5.04 (1H, t, J 7.5, CH=C), 4.44 (1H, ddd, J11, 5.5, 1.5, CHNH), 3.24-3.16 (2H, m, CH₂NH), 2.20 (1H, dd, J14.5, 7.5, C=CHCH₂), 2.15 (1H, dd, J, 14.5, 7.5, C-CHCH₂), 2.03-1.90 (2H, m, 2 x ring CH), 1.84-1.72 (2H, m, 2 x ring CH), 1.65 (3H, s, CH₃), 1.56 (3H, s, CH₃), 1.45-1.28 (2H, m, 2 x ring CH), 1.13 (3H, s, CH₃) and 1.12 (3H, s, CH₃); δ_{C} (125 MHz, CDCl₃) 176.9, 176.0 (CO), 134.1, 119.9 (CH=CH), 52.1 (NHCHCO), 42.5 (CH₂CMe₂), 42.1 (CH₂N), 39.0, 31.5, 28.9, 28.0 (CH₂ lactam), 26.0, 25.0, 24.9, 17.9 (CH₃); m/z (MH⁺ C₁₅H₂₇N₂O₂ requires 267.2073) 267.2063.

Step 4

Example 24: (S)-3-(2,2',5'-Trimethyl-hexanoyl)amino-caprolactam: (S)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam (400 mg) was dissolved in EtOAc (25 ml), palladium hydroxide-on-carbon (20%, ca 100 mg) was added, and the mixture was stirred at ambient temperature under an atmosphere of hydrogen for 14 hours. The reaction was then filtered through a Celite® pad and the solvent was removed in vacuo to give (6)-3-(2',2',5'-trimethyl-hexanoyl)aminocaprolactam as a waxy solid (400 mg, 98%). (S)-3-(2,2',5'-Trimethyl-hexanoyl)amino-caprolactam, Yield (400 mg, 98%). m.p. 73-74 °C; $[\alpha]_{25D}^{25} (c=1, \text{CHCl}_3) +27.8$; $\nu_{\text{max}}/\text{cm}^{-1}$ 3249 (NH), 1654, 1638 (CO), 1502 (NH); δ_{H} (500 MHz, CDCl_3) 7.08 (1H, d, J 5.0, CHNH), 6.75-6.55 (1H, br m, CH_2NH), 4.44 (1H, ddd, J 11, 5.5, 1.5, CHNH), 3.29-3.16 (2H, m, CH_2NH), 2.03-1.91 (2H, m, 2 × ring CH), 1.84-1.73 (2H, m, 2 × ring CH), 1.47-1.28 (5H, m, 2 × ring CH + CH_2 + $\text{CH}(\text{CH}_3)_2$), 1.13 (3H, s, CH_3), 1.12 (3H, s, CH_3), 1.08-1.02 (2H, m, CH_2), 0.82 (3H, s, CH_3), 0.80 (3H, s, CH_3); δ_{C} (125 MHz, CDCl_3) 177.1, 176.1 (CO), 52.1 (NHCHCO), 42.1 (CH_2N), 41.9 (CH_2CMe_2), 39.0, 33.7, 31.5, 28.9 (CH_2), 28.4 (Me_2CH), 27.9 (CH_2), 25.3, 25.2, 22.6, 22.5 (CH_3); m/z (MH^+ $\text{C}_{15}\text{H}_{29}\text{N}_2\text{O}_2$ requires 269.2229) 269.2219.

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3. 3 Steps

Overview

Steps/Stages

- 1.1 R:NaOH, S:H₂O, S:EtOH, 6 h, reflux; cooled
- 1.2 R:Cl(O=)CC(=O)Cl, C:DMF, S:CH₂Cl₂, 1 h
- 2.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 12 h, rt
- 3.1 R:H₂, C:Pd(OH)₂, S:AcOEt, 14 h, rt

Notes

1) reaction from p.38 in patent, 2) reaction from p.30 in patent, 3) reaction from p.30 in patent, Reactants: 2, Reagents: 4, Catalysts: 2, Solvents: 4, Steps: 3, Stages: 4, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Step 1

2,2,5-Trimethyl-hex-4-enoyl chloride: methyl 2,2,5-trimethyl-hex-4-enoate (2.74 g, 16 mmol) was dissolved in ethanol (50 ml) and added to a solution of NaOH (3.0 g, 75 mmol) in water (35 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacua*. The residue was partitioned between pH 2 aqueous buffer (0.5 M NaHSO₄ / 0.5 M Na₂SO₄) and diethyl ether (3x150 ml). The combined organic layers were dried over Na₂CO₃ and the ether solvent removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoic acid (>95% pure) as a colourless oil. The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoyl chloride which was all used without purification in the next step. **2,2,5-Trimethyl-hex-4-enoyl chloride.**

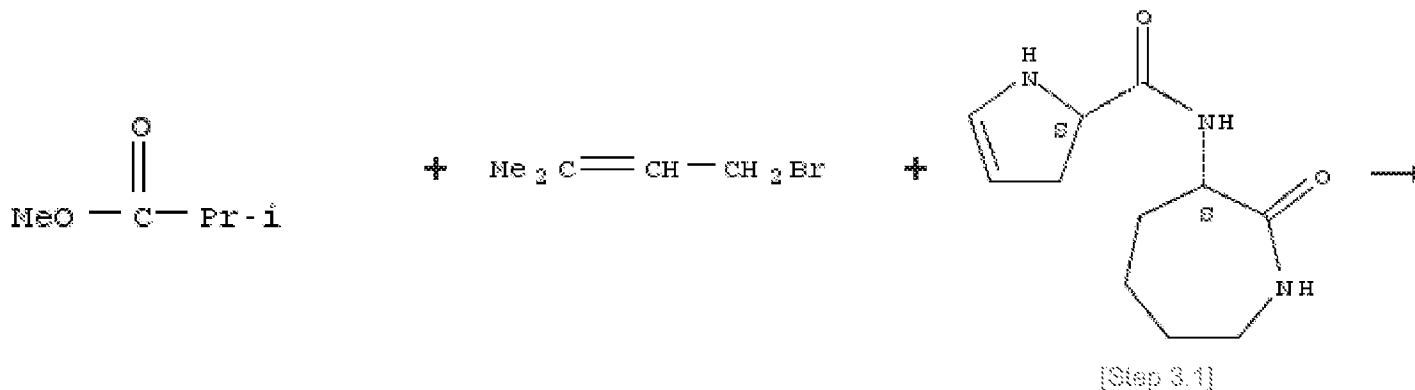
Step 2

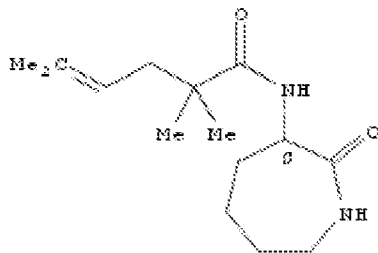
Example 23: (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactamhydro-pyrrolidine-5-carboxylate (4.11 g, 16 mmol) and Na₂CO₃ (5.09 g, 48 mmol) in water (50 ml) were added to a solution of 2,2,5-trimethyl-hex-4-enoyl chloride (16 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 50 ml). The combined organic layers were dried over Na₂CO₃ and reduced *in vacua*. The residue was purified by silica column chromatography (1:5 EtOAc: hexanes to EtOAc) to give (S)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam as a waxy solid (3.58 g, 84%). (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam, Yield (3.58 g, 84%). m.p. 43-44 °C; [α]_D²⁵ (c = 1, CHCl₃) +23.2; ν_{max} /cm⁻¹ 3394, 3251 (NH), 1674, 1633 (CO), 1503 (NH); δ H (500 MHz, CDCl₃) 7.11 (1H, d, J 5.0, CHNH), 6.65-6.45 (1H, br m, CH₂NH), 5.04 (1H, t, J 7.5, CH=C), 4.44 (1H, ddd, J 11, 5.5, 1.5, CHNH), 3.24-3.16 (2H, m, CH₂NH), 2.20 (1H, dd, J 14.5, 7.5, C=CHCH₂), 2.15 (1H, dd, J, 14.5, 7.5, C-CHCH₂), 2.03-1.90 (2H, m, 2 x ring CH), 1.84-1.72 (2H, m, 2 x ring CH), 1.65 (3H, s, CH₃), 1.56 (3H, s, CH₃), 1.45-1.28 (2H, m, 2 x ring CH), 1.13 (3H, s, CH₃) and 1.12 (3H, s, CH₃); δ c (125 MHz, CDCl₃) 176.9, 176.0 (CO), 134.1, 119.9 (CH=CH), 52.1 (NHCHCO), 42.5 (CH₂CMe₂), 42.1 (CH₂N), 39.0, 31.5, 28.9, 28.0 (CH₂ lactam), 26.0, 25.0, 24.9, 17.9 (CH₃); m/z (MH⁺ C₁₅H₂₇N₂O₂ requires 267.2073) 267.2063.

Step 3

Example 24: (S)-3-(2',2',5'-Trimethyl-hexanoyl)amino-caprolactam: (S)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam (400 mg) was dissolved in EtOAc (25 ml), palladium hydroxide-on-carbon (20%, ca 100 mg) was added, and the mixture was stirred at ambient temperature under an atmosphere of hydrogen for 14 hours. The reaction was then filtered through a Celite® pad and the solvent was removed *in vacua* to give (S)-3-(2',2',5'-trimethyl-hexanoyl)aminocaprolactam as a waxy solid (400 mg, 98%). (S)-3-(2',2',5'-Trimethyl-hexanoyl)aminocaprolactam, Yield (400 mg, 98%). m.p. 73-74 °C; [α]_D²⁵ (c=1, CHCl₃) +27.8; ν_{max} /cm⁻¹ 3249 (NH), 1654, 1638 (CO), 1502 (NH); δ H (500 MHz, CDCl₃) 7.08 (1H, d, J 5.0, CHNH), 6.75-6.55 (1H, br m, CH₂NH), 4.44 (1H, ddd, J 11, 5.5, 1.5, CHNH), 3.29-3.16 (2H, m, CH₂NH), 2.03-1.91 (2H, m, 2 x ring CH), 1.84-1.73 (2H, m, 2 x ring CH), 1.47-1.28 (5H, m, 2 x ring CH + CH₂ + CH(CH₃)₂), 1.13 (3H, s, CH₃), 1.12 (3H, s, CH₃), 1.08-1.02 (2H, m, CH₂), 0.82 (3H, s, CH₃), 0.80 (3H, s, CH₃); δ c (125 MHz, CDCl₃) 177.1, 176.1 (CO), 52.1 (NHCHCO), 42.1 (CH₂N), 41.9 (CH₂CMe₂), 39.0, 33.7, 31.5, 28.9 (CH₂), 28.4 (Me₂CH), 27.9 (CH₂), 25.3, 25.2, 22.6, 22.5 (CH₃); m/z (MH⁺ C₁₅H₂₉N₂O₂ requires 269.2229) 269.2219.

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4. 3 Steps



Overview

Steps/Stages

- 1.1 R:LiN(Pr-i)₂, S:THF, 1 h, -78°C
- 1.2 14 h, -78°C → rt
- 2.1 R:NaOH, S:H₂O, S:EtOH, 6 h, reflux; cooled
- 2.2 R:Cl(O=)CC(=O)Cl, C:DMF, S:CH₂Cl₂, 1 h
- 3.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 12 h, rt

Notes

1) reaction from p.37 in patent, 2) reaction from p.38 in patent, 3) reaction from p.30 in patent, Reactants: 3, Reagents: 4, Catalysts: 1, Solvents: 4, Steps: 3, Stages: 5, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Step 1

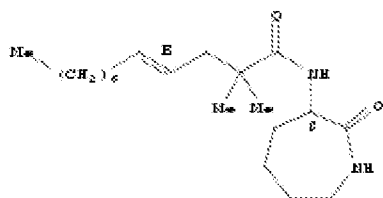
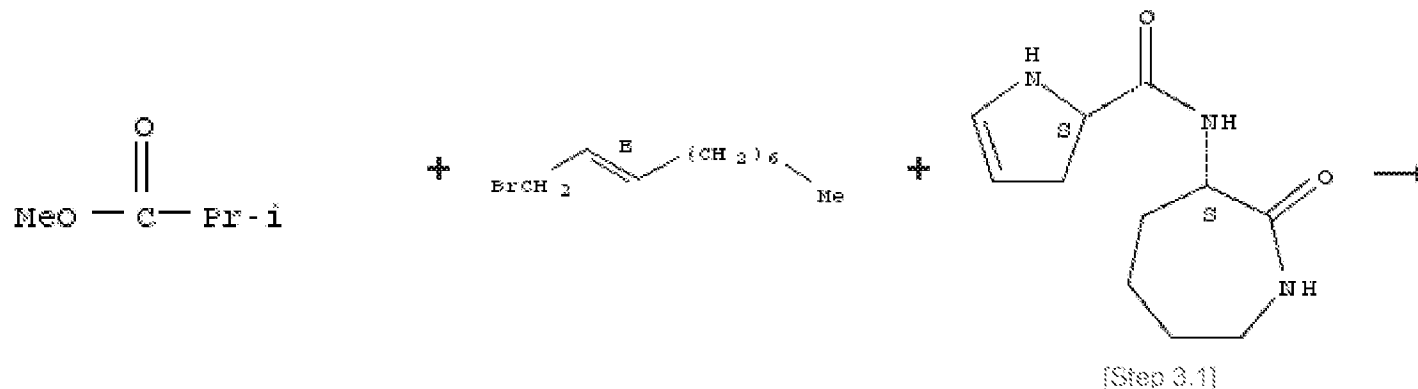
Methyl 2,2,5-trimethyl-hex-4-enoate: butyllithium (2.9 M, 50 mmol) was added to a solution of diisopropylamine (7.2 ml, 50 mmol) in dry THF (200 ml) at -78 °C under N₂. The reaction was stirred at -78 °C for 20 minutes and then methyl isobutyrate (5.7 ml, 50 mmol) was added. The reaction was stirred at -78 °C for 1 hour, and then 3-methyl-but-2-enyl bromide (5.8 ml, 50 mmol) was added and the reaction was allowed to warm to ambient temperature over 14 hours. The reaction solvent was then removed in vacuo, and the residue was partitioned between pH 2 aqueous buffer (0.5 M NaHSO₄ / 0.5 M Na₂SO₄) and hexane (3 x 250 ml). The combined organic layers were dried over Na₂SO₄ and the hexane solvent removed in vacuo to give methyl 2,2,5-trimethyl-hex-4-enoate as a colourless oil (6.93 g 81%). Methyl 2,2,5-trimethyl-hex-4-enoate, Yield (6.93 g 81%). ν_{max} /cm⁻¹ 1732 (CO); δ H (400 MHz, CDCl₃) 5.04 (1H, tsept, J7.5, 1.5, CH=C), 3.63 (3H, s, OCH₃), 2.20 (2H, d, J7.5, CHCH₂), 1.68 (3H, br s, CH=CMeMe), 1.58 (3H, br s, CH=CMeMe), 1.14 (6H, s, (CH₃)₂CO); δ C (125 MHz, CDCl₃) 178.4 (CO), 134.1 (Me₂OCH), 119.8 (Me₂C=CH), 51.6 (OCH₃), 42.8 (Me₂CCO), 38.7 (CH₂), 25.9, 24.7 (x 2), 17.8 (CCH₃); m/z (MH⁺ C₁₀H₁₉O₂ requires 171.1385) 171.1388.

Step 2

2,2,5-Trmiethyl-hex-4-enoyl chloride: methyl 2,2,5-trimethyl-hex-4-enoate (2.74 g, 16 mmol) was dissolved in ethanol (50 ml) and added to a solution of NaOH (3.0 g, 75 mmol) in water (35 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacua*. The residue was partitioned between pH 2 aqueous buffer (0.5 M NaHSO₄ / 0.5 M Na₂SO₄) and diethyl ether (3x150 ml). The combined organic layers were dried over Na₂CO₃ and the ether solvent removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoic acid (>95% pure) as a colourless oil. The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoyl chloride which was all used without purification in the next step. **2,2,5-Trmiethyl-hex-4-enoyl chloride.**

Example 23: (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactamhydro-pyrrolidine-5-carboxylate (4.11 g, 16 mmol) and Na₂CO₃ (5.09 g, 48 mmol) in water (50 ml) were added to a solution of 2,2,5- trimethyl-hex-4-enoyl chloride (16 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 50 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacua. The residue was purified by silica column chromatography (1:5 EtOAc: hexanes to EtOAc) to give (5)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam as a waxy solid (3.58 g, 84%). (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam, Yield (3.58 g, 84%). m.p. 43-44 °C; [α]_D²⁵ (c = 1, CHCl₃) +23.2; ν_{max}/cm⁻¹ 3394, 3251 (NH), 1674, 1633 (CO), 1503 (NH); δ_H (500 MHz, CDCl₃) 7.11 (1H, d, J_{5,6}, CHNH), 6.65-6.45 (1H, br m, CH₂NH), 5.04 (1H, t, J 7.5, CH=C), 4.44 (1H, ddd, J₁₁, 5.5, 1.5, CHNH), 3.24-3.16 (2H, m, CH₂NH), 2.20 (1H, dd, J_{14,5}, 7.5, C=CHCH₂), 2.15 (1H, dd, J, 14.5, 7.5, C-CHCH₂), 2.03- 1.90 (2H, m, 2 × ring CH), 1.84-1.72 (2H, m, 2 × ring CH), 1.65 (3H, s, CH₃), 1.56 (3H, s, CH₃), 1.45-1.28 (2H, m, 2 × ring CH), 1.13 (3H, s, CH₃) and 1.12 (3H, s, CH₃); δ_c (125 MHz, CDCl₃) 176.9, 176.0 (CO), 134.1, 119.9 (CH=C), 52.1 (NHCHCO), 42.5 (CH₂CMe₂), 42.1 (CH₂N), 39.0, 31.5, 28.9, 28.0 (CH₂ lactam), 26.0, 25.0, 24.9, 17.9 (CH₃); m/z (MH⁺ C₁₅H₂₇N₂O₂ requires 267.2073) 267.2063.

5. 3 Steps



Steps/Stages

- 1.1 R:LiN(Pr-*i*)₂, S:THF, 1 h, -78°C
- 1.2 14 h, -78°C → rt
- 2.1 R:NaOH, S:H₂O, S:EtOH, 6 h, reflux; cooled
- 2.2 R:Cl(O=)CC(=O)Cl, C:DMF, S:CH₂Cl₂, 1 h
- 3.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 12 h, rt

1) reaction from p.36 in patent, 2) reaction from p.37 in patent, 3) reaction from p.29 in patent, Reactants: 3, Reagents: 4, Catalysts: 1, Solvents: 4, Steps: 3, Stages: 5, Most stages in any one step: 2

Preparation of 3-aminocaprolactam
derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun
2005

Experimental Procedure

Step 1

(E)-Methyl 2,2-dimethyl-dodec-4-enoate: butyllithium (3.8 M, 10 mmol) was added to a solution of diisopropylamine (1.42 ml, 10 mmol) in dry THF at -78 °C under N₂. The reaction was stirred at -78 °C for 20 minutes and then methyl isobutyrate (1.15 ml, 10 mmol) was added. The reaction was stirred at -78 °C for 1 hour, and then (E)-dec-2-enyl bromide (2.19g, 10 mmol) was added and the reaction was allowed to warm to ambient temperature over 14 hours. The reaction solvent was then removed in vacua, and the residue was partitioned between pH 2 aqueous buffer (0.5 M NaHSO₄ / 0.5 M Na₂SO₄) (100 ml) and hexane (3 x 100 ml). The combined organic layers were dried over Na₂SO₄ and the hexane solvent removed in vacuo to give crude (E)-methyl 2,2-dimethyl-dodec-4-enoate (>90% pure) (2.27 g) as a colourless oil (E)-Methyl 2,2-dimethyl-dodec-4-enoate, Yield (2.27 g). $\nu_{\max}/\text{cm}^{-1}$ 1734 (CO); δ_{H} (400 MHz, CDCl₃) 5.42 (1H, br dt, J 15, 6.5, CH=CH), 5.30 (1H, dt, J 15, 7, 1, CH=CH), 3.64 (3H, s, OCH₃), 2.18 (2H, dd, J 7, 1, CH₂CMe₂), 1.96 (2H, br q, J 6.5, CH₂CH₂CH=CH), 1.35-1.20 (10H, m, (CH₂)₈CH₃), 1.14 (6H, s, C(CH₃)₂), 0.87 (3H, t, J 6.5, CH₂CH₃) δ_{C} (125 MHz, CDCl₃) 178.2 (CO), 134.1, 125.2 (HC-CH), 51.5 (OCH₃), 43.6 (CH₂), 42.6 (Me₂CCO), 32.6, 31.8, 29.5, 29.1, 29.0 (CH₂), 24.7 (C(CH₃)₂), 22.6 (CH₂), 14.1 (CH₂CH₃); m/z (MH⁺ C₁₅H₂₉N₂O₂ requires 241.2168) 241.2169.

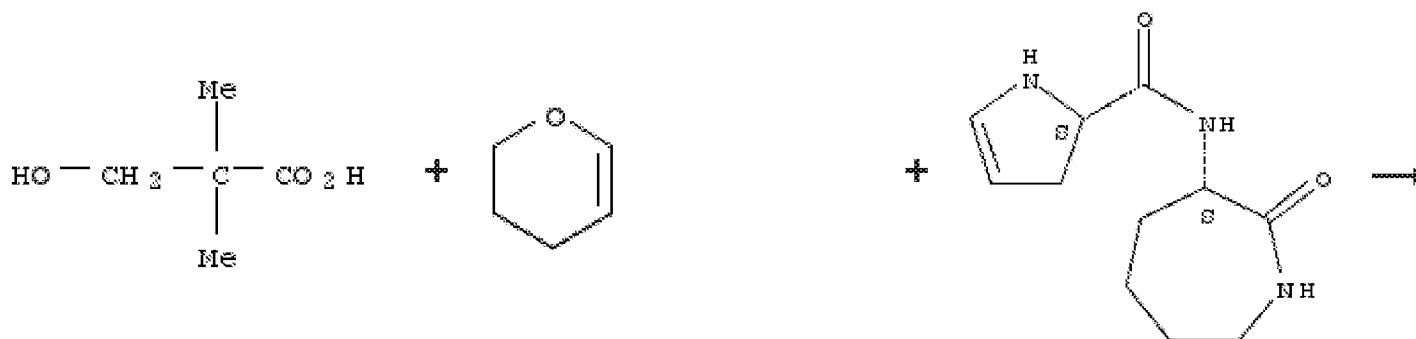
Step 2

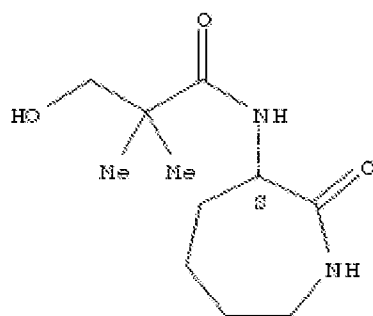
(E)-2,2-Dimethyl-dodec-4-enoyl chloride: the entire product from the above reaction was then dissolved in ethanol (50 ml) and added to a solution of NaOH (2.0 g, 50 mmol) in water (25 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacuo*. The residue was partitioned between pH 2 aqueous buffer (0.5 M NaHSO₄ / 0.5 M Na₂SO₄) (100 ml) and diethyl ether (3 x 100 ml). The combined organic layers were dried over Na₂SO₄ and the ether solvent removed *in vacuo* to give crude (E)-2,2-dimethyl-dodec-4-enoic acid (>90% pure) as a colourless oil. The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacuo* to give crude (E)-2,2-dimethyl-dodec-4-enoyl chloride which was all used without purification in the next step. (E)-2,2-Dimethyl-dodec-4-enoyl chloride

Step 3

Example 22: (S,E)-3-(2',2'-Dimethyl-dodec-4'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (10 mmol) and Na₂CO₃ (3.0 mmol) in water (3.0 ml) were added to a solution of 2,2-dimethyl-dodec-2-enoyl chloride (crude, from above reaction) (10 mmol) in dichloromethane (30 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacuo. The residue was purified by silica column chromatography (1:1 EtOAc: hexanes to EtOAc) to give (S,E)-3-(2',2'-dimethyl-dodec-4'-enoyl)amino-caprolactam as a colourless oil (2.12 g, 63%). (S,E)-3-(2',2'-Dimethyl-dodec-4'-enoyl)amino-caprolactam, Yield (2.12 g, 63%). $[\alpha]_{\text{D}}^{25}$ (c = 1, CHCl₃ +21.6; $\nu_{\max}/\text{cm}^{-1}$ 3264 (NH), 1639 (CO), 1497 (NH); δ_{H} (500 MHz, CDCl₃) 7.09 (1H, d, J 5.5, CHNH), 6.67-6.32 (1H, br m, CH₂NH), 5.42 (1H, dt, J 15, 6.5, CH=CH), 5.28 (1H, dt, J 15, 7, CH=CH), 4.44 (1H, dd, J 11, 5.5, CHNH), 3.30-3.17 (2H, m, CH₂NH), 2.20 (1H, dd, J 13.5, 7, CH=CHCH₂), 2.14 (1H, dd, J 13.5, 7, CH=CHCH₂), 2.01-1.87 (4H, br m, ring CH x2, + CH₂CH=CH), 1.87-1.74 (2H, m, ring CH), 1.47-1.32 (2H, m, ring CH), 1.27-1.15 (10H, br m, (CH₂)₈CH₃) 1.13 (3H, s, CMeMe), 1.12 (3H, s, CMeMe) and 0.83 (3H, t, J 7, CH₂CH₃); δ_{C} (125 MHz, CDCl₃) 176.8, 176.0 (CO), 134.2, 125.2 (CH=CH), 52.1 (NHCHCO), 43.9 (CH₂), 42.1 (x2)(CH₂+ CMe₂), 32.6, 31.8, 31.5, 30.1, 29.4, 29.1 (x2), 28.9, 27.9 (CH₂), 25.0, 24.8 (CH₃) and 22.6 (CH₃); m/z (MH⁺ C₂₀H₃₇N₂O₂ requires 337.2855) 337.2858.

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6. 2 Steps



Overview

Steps/Stages

- 1.1 R:p-MeC₆H₄SO₃H, S:CH₂Cl₂, 3 h, rt
- 1.2 R:KOH, S:H₂O, S:EtOH, 18 h, reflux
- 1.3 S:H₂O, pH 2
- 2.1 R:1-Benzotriazolol, R:Diimidazolylketone, S:THF, 4 h, reflux; reflux
→ rt
- 2.2 R:Disodiumcarbonate, S:H₂O, 18 h, rt
- 2.3 R:AcCl, S:MeOH, 18 h, rt

Notes

1) regioselective in stage 1, Na₂SO₄/NaHSO₄ buffer used in stage 3, reaction from p.47 in patent, 2) reaction from p.48 in patent, Reactants: 3, Reagents: 6, Solvents: 5, Steps: 2, Stages: 6, Most stages in any one step: 3

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 15 Jun 2005

Experimental Procedure

Step 1

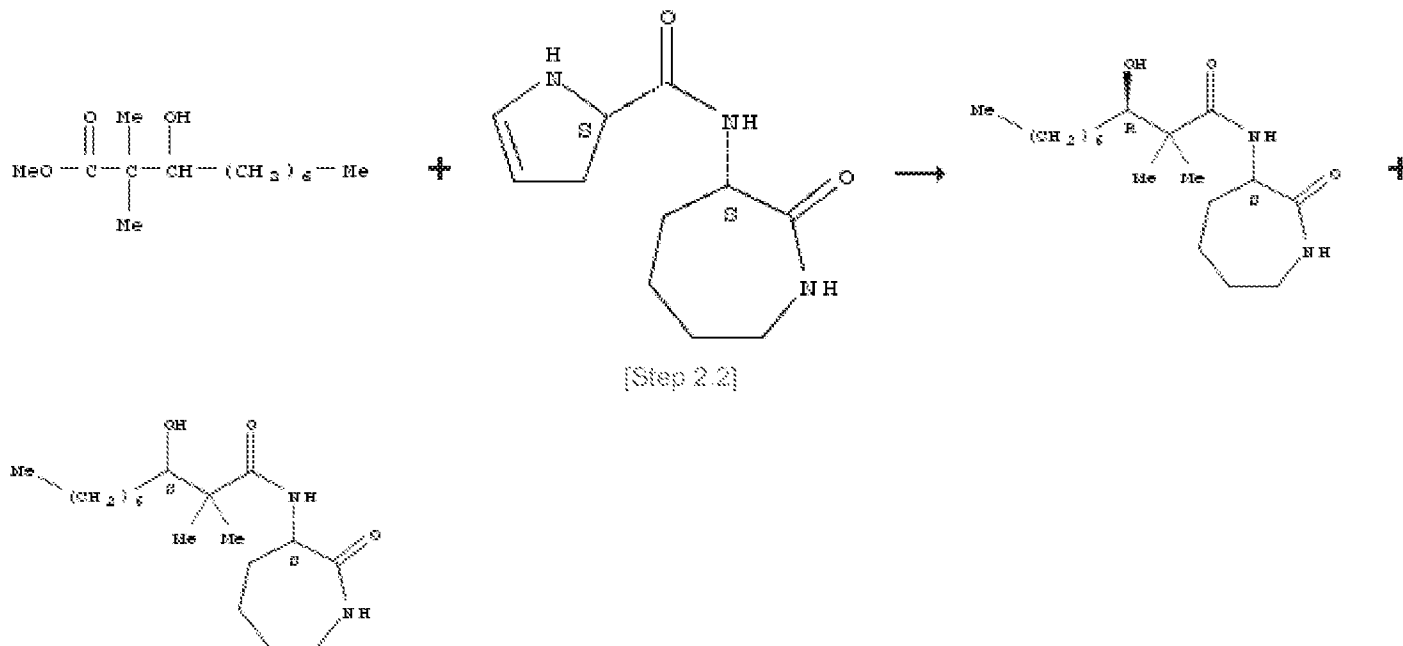
Example 60: 2,2-Dimethyl-3-(tetrahydropyran-2-yloxy)-propionic acid (Intermediate) 2,2-Dimethyl-3-hydroxy propionic acid (100 mmol) and 3,4-dihydro-2H-pyran (210 mmol) were dissolved in dichloromethane (50 ml), and para-toluenesulfonic acid (10 mg) was added and the reaction was stirred at ambient temperature for 3 hours. The reaction solvent was then removed and the residue was dissolved in ethanol (100 ml). A solution of KOH (120 mmol) in water (30 ml) was added and the reaction was heated at reflux for 18 hours. The reaction solvent was removed in vacua and the residue was partitioned between water and diethyl ether. The aqueous layer was acidified with pH 2 buffer (0.5 M Na₂SO₄ / 0.5 M NaHSO₄) and then extracted with diethyl ether. The diethyl ether layer was then dried over Na₂SO₄ and the solvent was removed in vacuo to give 2,2-dimethyl-3-(tetrahydropyran-2-yloxy)-propionic acid as an oil (20.0 g, >95%). 2,2-Dimethyl-3-(tetrahydropyran-2-yloxy)-propionic acid, Yield (20.0 g, >95%). δ H (400 MHz, CDCl₃) 4.62 (1H, t, J 3.5, CHO₂), 3.82 (1H, ddd, J 12, 9, 3, ring CH₂O), 3.75 (1H, d, J 12, chain CH₂O), 3.55-3.46 (1H, m, ring CH₂O), 3.40 (1H, d, J 12, chain CH₂O), 1.90-1.45 (6H, m, (CH₂)₃), 1.25 (3H, s, CH₃) and 1.23 (3H, s, CH₃).

Step 2

Example 61: (S)-(2',2'-Dimethyl-3'-hydroxy-propionyl)amino-caprolactam 2,2-Dimethyl-3-(tetrahydropyran-2-yloxy)-propionic acid (4.65 mmol), 1-hydroxybenzotriazole monohydrate (4.65 mmol) and carbonyl diimidazole (4.50 mmol) were dissolved in THF (30 ml) and the reaction was heated at reflux for 4 hours. After the reaction was cooled to ambient temperature, a solution of (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (5 mmol) and Na₂CO₃ (15 mmol) in water (30 ml) was added and the reaction was stirred for 18 hours. The THF was then removed from the reaction by distillation in vacuo and the aqueous layer was extracted with ethyl acetate. The ethyl acetate layer was dried over Na₂SO₄ and reduced in vacuo. The residue was dissolved in MeOH, and acetyl chloride (1 ml) was added. The reaction was stirred at ambient temperature for 18 hours, and then reduced in vacuo to give (S)- (2'-dimethyl-3'-hydroxy propionyl)amino-caprolactam as a solid (854 mg, 83%). (S)-(2',2'-Dimethyl-3'-hydroxy-propionyl)amino-caprolactam, Yield (854 mg, 83%). m.p. 97-99 °C; $[\alpha]_{25D}$ (c = 0.5, CHCl₃) +30.0; δ H (400 MHz, CDCl₃) 7.24 (1H, d, J 5.0, CHNH), 6.38 (1H, br s, CH₂NH), 4.49 (1H, dd, J 10, 6, CHNH), 3.54 (1H, d, J 11, CHHOH), 3.49 (1H, d, J 11, CHHOH), 3.33-3.20 (2H, m, CH₂NH), 2.03-1.96 (2H, m, 2 × ring CH), 1.87-1.72 (2H, m, 2 × ring CH), 1.50-1.30 (2H, m, 2 × ring CH), 1.20 (3H, s, CH₃) and 1.18 (3H, s, CH₃); δ c (125 MHz, CDCl₃) 177.2, 176.0 (CO), 69.9 (CHOH), 52.1 (NHCHCO), 43.2 (CCO), 41.9 (CH₂N), 31.1, 28.8, 27.9 (CH₂ lactam), 22.4 and 22.3 (CH₃).

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7. 2 Steps



Overview

Steps/Stages

- 1.1 R:KOH, S:H₂O, S:EtOH, 18 h, reflux; cooled
- 1.2 S:H₂O, pH 2
- 2.1 R:1-Benzotriazolol, R:EtN=C=N(CH₂)₃NMe₂•HCl, S:THF, 4 h, rt
- 2.2 R:Disodiumcarbonate, S:H₂O, 18 h, rt

Notes

1) Na₂SO₄/NaHSO₄ buffer used in stage 2, reaction from p.46 in patent, 2) stereoselective, combined yield = 88%, reaction from p.47 in patent, Reactants: 2, Reagents: 4, Solvents: 3, Steps: 2, Stages: 4, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

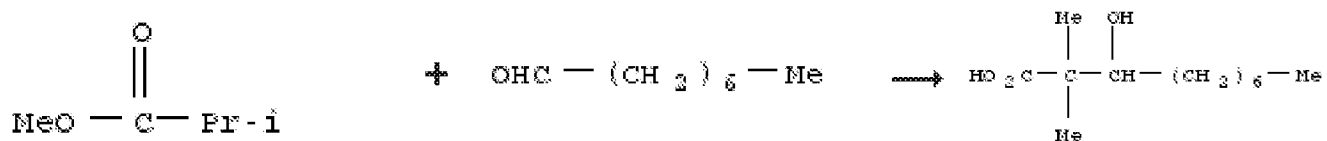
Step 1

Example 58: 2,2-Dimethyl-3-hydroxy decanoic acid (Intermediate). Methyl 2,2-dimethyl-3-hydroxy decanoate (20 mmol) was dissolved in EtOH (80 ml) and a solution of KOH (40 mmol) in water (20 ml) was added. The reaction was heated at reflux for 18 hours, and then the reaction was allowed to cool. The solvent was removed in vacuo and the residue was partitioned between water and diethyl ether. The aqueous layer was then acidified with pH 2 buffer (0.5 M Na₂SO₄ / 0.5 M NaHSO₄ and extracted with diethyl ether. The solution was dried over Na₂SO₄ and rediced in vacuo to give 2,2-dimethyl-3-hydroxy decanoic acid which solidified on standing 2,2-Dimethyl-3-hydroxy decanoic acid (Intermediate) m.p. 39-41 °C; ¹H (400 MHz, CDCl₃) 3.64 (1H, dd, J10, 2, CHOH), 1.67-1.12 (22H, m, (CH₂)₈ + C(CH₃)₂) and 0.88 (3H, t, J7, CH₂CH₃).

Step 2

Example 59(a): (3S,3'R) and Example 59(b): (3S,3'S)-3-(3'-Hydroxy-2',2'-dimethyldecanoyl)aminocaprolactam: 2,2-Dimethyl-3-hydroxy decanoic acid (1.77 mmol) and 1-hydroxybenzotriazole monohydrate (1.77 mmol) were dissolved in THF (10 ml). 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.77 mmol) was added and the reaction was stirred at ambient temperature for 4 hours. A solution of (S,S)-3- amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (2 mmol) and Na₂CO₃ (6 mmol) in water (15 ml) was added and the reaction was stirred for 18 hours. The reaction solvent was then removed in vacua and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with pH 2 buffer (0.5 M Na₂SO₄ / 0.5 M NaHSO₄ and dilute aqueous sodium hydroxide, and then dried over Na₂SO₄ and reduced in vacua. The residue was chromatographed on silica gel (25% ethyl acetate in hexanes to 100% ethyl acetate) to give a mixture of (3S,3R) and (3S,3'S)-3-(3'-hydroxy-2',2'-dimethyldecanoyl)aminocaprolactams (557 mg, 88%). Example 59(a): (3S,3'R) and Example 59(b): (3S,3'S)-3-(3'-Hydroxy-2',2'-dimethyldecanoyl)aminocaprolactam, Yield (557 mg, 88%). δ H (500 MHz, CDCl₃) 7.28 (1H, d, J 6, NHCH one isomer), 7.25 (1H, d, J 6, NHCH, one isomer), 6.62-6.48 (1H, br m, NHCH₂, both isomers), 4.53-4.42 (1H, m, NCH, both isomers), 3.77 (1H, br d, J, 6, OH, one isomer), 3.63 (1H, br d, J, 6, OH, one isomer), 3.47-3.36 (1H, m, CHOH, both isomers), 3.32-3.17 (2H, m, NCH₂, both isomers), 2.07-1.92 (2H, m, lactam CH x2, both isomers), 1.87-1.71 (2H, m, lactam CH x2, both isomers), 1.60- 1.17 (21H, m, lactam CH x2 + chain (CH₂)₈ + CH₃, both isomers), 1.14 (3H, s, CCH₃, both isomers) and 0.84 (3H, t, J 7, CH₂CH₃, both isomers); δ c (125 MHz, CDCl₃) 177.6, 177.2, 175.8 (CO, both isomers), 77.8, 77.4 (CHOH), 52.1 (NCH, both isomers), 45.9, 45.8 (C(CH₃)₂), 42.1, 42.0 (NCH₂), 31.9 (x2) 31.6, 31.3, 30.9, 29.6 (x4), 29.3, 28.8, 27.9, 26.7, 26.6, 22.6 (CH₂), 23.7, 23.5, 21.1, 20.4 and 14.1 (CH₃).

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8. 2 Steps

Overview

Steps/Stages

- 1.1 R:LiN(Pr-i)₂, S:THF, 45 min, -78°C
- 1.2 18 h, -78°C → rt
- 1.3 R:NH₄Cl, S:H₂O, rt
- 2.1 R:KOH, S:H₂O, S:EtOH, 18 h, reflux; cooled
- 2.2 S:H₂O, pH 2

Notes

1) reaction from p.46 in patent, 2)
Na₂SO₄/NaHSO₄ buffer used in stage 2,
reaction from p.46 in patent, Reactants: 2,
Reagents: 3, Solvents: 3, Steps: 2, Stages: 5,
Most stages in any one step: 3

References

Preparation of 3-aminocaprolactam
derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 15 Jun
2005

Experimental Procedure

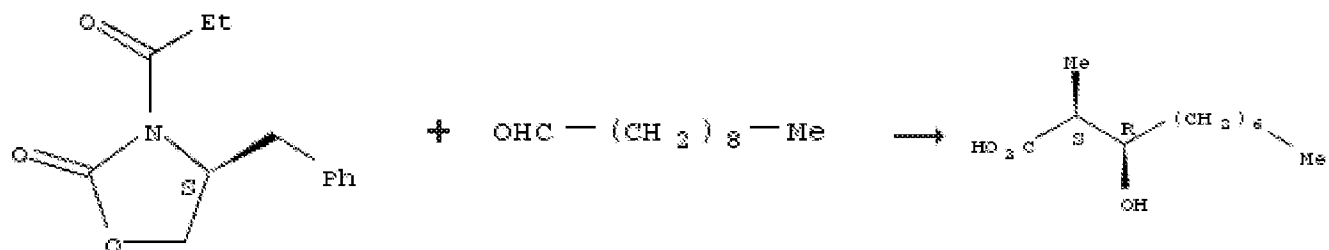
Step 1

Example 57; Methyl 2,2-dimethyl-3-hydroxy decanoate (Intermediate), Butyllithium (2.5 M in hexanes, 50 mmol) was added to a solution of diisopropylamine (50 mmol) in dry THF (200 ml) at -78 °C under an atmosphere of dry nitrogen. The reaction was stirred for 30 minutes, and then methyl isobutyrate (50 mmol) was added. After 45 minutes, decanal (50 mmol) was added and the reaction was allowed to warm to ambient temperature over 18 hours. After the addition of saturated aqueous ammonium chloride (10 ml), the reaction solvent was removed in vacuo and the residue was partitioned between hexanes and pH 2 buffer (0.5 M Na₂SO₄ / 0.5 M NaHSO₄). The organic layer was dried over Na₂SO₄ and the solvent was removed to give methyl 2,2-dimethyl-3-hydroxy decanoate as an oil (9.98g, 77%). Methyl 2,2-dimethyl-3-hydroxy decanoate (Intermediate), Yield (9.98g, 77%). δ H (400 MHz, CDCl₃) 3.70 (3H, s, OCH₃), 3.69 (1H, dd, J10, 2, CHOH), 1.68-1.20 (16H, m, (CH₂)₈), 1.19 (3H, s, CCH₃), 1.17 (3H, s, CCH₃) and 0.88 (3H, t, J 7, CH₂CH₃) (no OH observed).

Step 2

Example 58: 2,2-Dimethyl-3-hydroxy decanoic acid (Intermediate). Methyl 2,2-dimethyl-3-hydroxy decanoate (20 mmol) was dissolved in EtOH (80 ml) and a solution of KOH (40 mmol) in water (20 ml) was added. The reaction was heated at reflux for 18 hours, and then the reaction was allowed to cool. The solvent was removed in vacuo and the residue was partitioned between water and diethyl ether. The aqueous layer was then acidified with pH 2 buffer (0.5 M Na₂SO₄ / 0.5 M NaHSO₄) and extracted with diethyl ether. The solution was dried over Na₂SO₄ and rediced in vacuo to give 2,2-dimethyl-3-hydroxy decanoic acid which solidified on standing 2,2-Dimethyl-3-hydroxy decanoic acid (Intermediate) m.p. 39-41 °C; δ H (400 MHz, CDCl₃) 3.64 (1H, dd, J10, 2, CHOH), 1.67-1.12 (22H, m, (CH₂)₈ + C(CH₃)₂) and 0.88 (3H, t, J7, CH₂CH₃).

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9. 2 Steps

Overview

Steps/Stages

- 1.1 R:TiCl₄, S:CH₂Cl₂, rt → -20°C; 15 min, -20°C
- 1.2 R:EtN(Pr-i)₂, 40 min
- 1.3 R:NMP, 10 min
- 1.4 1 h
- 2.1 R:LiOH, R:H₂O₂, S:H₂O, S:THF, 18 h, rt
- 2.2 S:H₂O, rt, pH 2

Notes

1) stereoselective in stage 4, aldol reaction, reaction from p.43 in patent, 2) Na₂SO₄/NaHSO₄ buffer used in stage 2, reaction from p.44 in patent, Reactants: 2, Reagents: 5, Solvents: 3, Steps: 2, Stages: 6, Most stages in any one step: 4

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

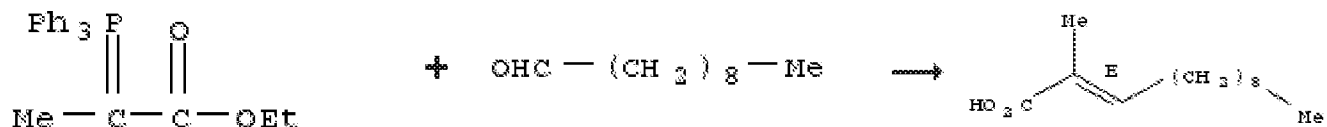
Step 1

Example 51: (4S,2'S,3'R)-4-Benzyl-3-(3'-hydroxy-2'-methyldecanoyl)-oxazolidin-2-one (Intermediate)
 This aldol reaction was performed according to published method (Crimmins M.T.; She, J.; Synlett, 2004, 1371-1374). (S)-4-Benzyl-3-propionyl-oxazolidin-2-one (5 mmol) (synthesised according to the method of Evans et al. Tetrahedron Lett., 1987, 28, 1123) was dissolved in CH₂Cl₂ (25 ml) and the solution was cooled to -20 °C under an atmosphere of dry nitrogen and TiCl₄ (5.25 mmol) was added. After 15 minutes, diisopropylethylamine (5.5 mmol) was added. After a further 40 minutes N-methylpyrrolidin-2-one (5.25 mmol) was added. After a further 10 minutes, decanal (5.5 mmol) was added and the reaction was stirred for 1 hour. Ammonium chloride solution was added and the reaction mixture was washed with pH 2 buffer (0.5 M Na₂SO₄ / 0.5 M NaHSO₄). The organic layer was dried over Na₂SO₄ and reduced in vacuo. The crude product was chromatographed on silica gel (10% to 33% ethyl acetate in hexane) to give (4S,2'S,3'R)-4-benzyl-3-(3'-hydroxy-2'-methyldecanoyl)-oxazolidin-2-one as an oil (1.34 g, 69%); (4S,2'S,3'R)-4-benzyl-3-(3'-hydroxy-2'-methyldecanoyl)-oxazolidin-2-one, yield (1.34 g, 69%); $\nu_{\text{max}}/\text{cm}^{-1}$ 1778 (NCO₂), 1697 (CON); δ_{H} (500 MHz, CDCl₃) 7.35-7.30 (2H, m, meta-Ph), 7.29-7.24 (1H, m, para-Ph), 7.21-7.17 (2H, m, ortho-Ph), 4.69 (1H, ddt, J 9.5, 7.5, 3.5, CHN), 4.21 (1H, t, J 9, OCHH), 4.17 (1H, dd, J 9, 3, OCHH), 3.93 (1H, ddd, J 7, 4.5, 3, CHOH), 3.75 (1H, qd, J 7, 2.5, CHCH₃), 3.24 (1H, dd, J 13.5, 3.5, CHHPH), 2.87 (1H, br s, CHOH), 2.78 (1H, dd, J 13.5, 9.5, CHHPH), 1.56-1.20 (19H, m, (CH₂)₈ + CHCH₃) and 0.86 (3H, t, J 7, CH₂CH₃); δ_{C} (125 MHz, CDCl₃) 177.6 (CCO), 153.0 (OCO), 135.0 (ipso-Ph), 129.4, 129.0 (ortho- + meta- Ph), 127.4 (para- Ph), 71.5 (CHOH), 66.1 (OCH₂), 55.1 (NCH), 42.1 (CHCH₃), 37.8, 33.8, 31.9, 29.6 (x3), 29.3, 26.0, 22.7 (CH₂), 14.1 and 10.3 (CH₃); m/z (MH⁺ C₂₃H₃₆NO₄ requires 390.2644) 390.2641.

Step 2

Example 53: (2S,3R)-3-Hydroxy-2-methyldecanoic acid (Intermediate) (4S,2'S,3'R)-4-Benzyl-3-(3'-hydroxy-2'-methyldecanoyl)-oxazolidin-2-one (1.42 mmol) was dissolved in THF (10 ml). Water (2 ml), aqueous hydrogen peroxide (8M, 0.5 mmol) and LiOH.H₂O (3 mmol) were added, and the reaction was stirred for 18 hours. Na₂SO₃ (10 mmol) was added and the reaction was extracted with ethyl acetate. The aqueous layer was then acidified with pH 2 buffer (0.5 M Na₂SO₄/0.5 M NaHSO₄), and extracted with diethyl ether. The diethyl ether layer was dried over Na₂SO₄ and reduced in vacuo to give crude (2S,3R)-3-hydroxy-2-methyldecanoic acid; This material was used directly in the synthesis of (3S,2'S,3'R)-3-(3'-hydroxy-2'-methyldecanoyl)amino-caprolactam. (2S,3R)-3-Hydroxy-2-methyldecanoic acid (Intermediate) δ_{H} (400 MHz, CDCl₃) 3.96-3.89 (1H, m, CHOH), 2.59 (1H, dq, J 7, 3, CHCH₃), 1.54- 1.36 (2H, m, CH₂), 1.36-1.22 (14H, m, (CH₂)₈) and 1.20 (3H, d, J 7, CHCH₃).

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10. 2 Steps

Overview

Steps/Stages

- 1.1 S:CH₂Cl₂, 18 h, rt
- 2.1 R:KOH, S:H₂O, S:EtOH, 18 h, reflux; cooled
- 2.2 R:HCl, S:H₂O, acidify

Notes

- 1) stereoselective, reaction from p.41 in patent, 2) reaction from p.42 in patent,
- Reactants: 2, Reagents: 2, Solvents: 3, Steps: 2, Stages: 3, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
 By Grainger, David John, Fox, David John
 From PCT Int. Appl., 2005053702, 15 Jun 2005

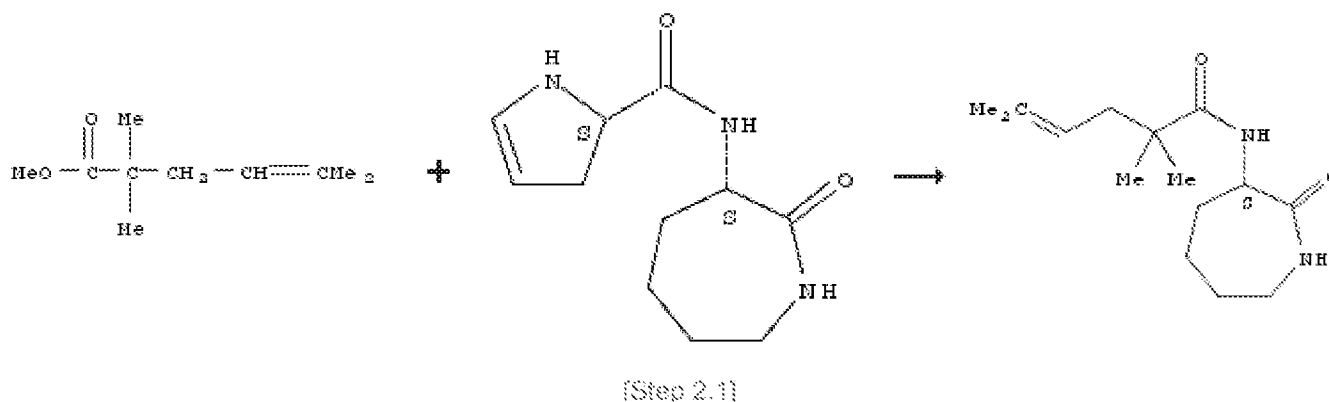
Step 1

Example 46: (E)-Ethyl 2-methyldodec-2-enoate (Intermediate). Decanal (5 mmol) and (carbethoxyethylidene)triphenylphosphorane (10 mmol) were dissolved in CH₂Cl₂ (20 ml) and the reaction was stirred for 18 hours. The solvent was then removed in vacua and the residue was filtered through a plug of silica gel with the aid of 5% diethyl ether in hexanes. The collected eluent was reduced in vacua to give (E)-ethyl 2-methyldodec-2-enoate as an oil (1.02 g, 88%). (E)-Ethyl 2-methyldodec-2-enoate, Yield (1.02 g, 88%). $\nu_{\text{max}}/\text{cm}^{-1}$ 1709 (CO), 1651 (C=C); δ_{H} (500 MHz, CDCl₃) 6.73 (1H, tq, J 7.5, 1.5, CH=C), 4.16 (2H, q, J 7, OCH₂), 2.13 (2H, br q, J 7.5, CH₂CH=C), 1.80 (3H, d, J 1.5, CH₃C=CH), 1.45-1.37 (2H, m, chain CH₂), 1.32-1.19 (15H, m, (CH₂)₆ + OCH₂CH₃) and 0.85 (3H, t, J 7, (CH₂)₈CH₃); δ_{C} (125 MHz, CDCl₃) 168.3 (CO), 142.4 (CH=C), 127.6 (CH=C), 60.3 (OCH₂), 31.8, 29.5, 29.4 (x2), 29.3, 28.6, 28.5, 22.6 (CH₂), 14.3, 14.1 and 12.3 (CH₃); m/z (MH+ C₁₅H₂₉O₂ requires 241.2168) 241.2165.

Step 2

Example 47: (E)-2-Methyldodec-2-enoic acid (Intermediate). (E)-Ethyl 2-methyldodec-2-enoate (1.43 mmol) was dissolved in ethanol (10 ml), and KOH (10 mmol) in water (5 ml) was added. The reaction was heated at reflux for 18 hours and then cooled. The solvent was removed in vacua and the residue partitioned between water and hexane. The aqueous layer was acidified with aqueous HCl, and was extracted with diethyl ether. The diethyl ether layer was dried over Na₂SO₄ and reduced in vacua to give (E)-2-methyldodec-2-enoic acid as a solid (308 mg, >95%) (E)-2-Methyldodec-2-enoic acid (Intermediate), Yield (308 mg, >95%). m.p. 28-31 °C; δ_{H} (400 MHz, CDCl₃) 6.91 (1H, tq, J 7.5, 1.5, CH=C), 2.18 (2H, br q, J 7.5, CH₂CH=C), 1.82 (3H, d, J 1.5, CH₃C=CH), 1.48-1.39 (2H, m, chain CH₂), 1.36-1.19 (12H, m, (CH₂)₆) and 0.88 (3H, t, J 7, (CH₂)₈CH₃) (no OH peak observed).

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11. 2 Steps

Overview

Steps/Stages

- 1.1 R:NaOH, S:H₂O, S:EtOH, 6 h, reflux; cooled
- 1.2 R:Cl(O=)CC(=O)Cl, C:DMF, S:CH₂Cl₂, 1 h
- 2.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 12 h, rt

Notes

1) reaction from p.38 in patent, 2) reaction from p.30 in patent, Reactants: 2, Reagents: 3, Catalysts: 1, Solvents: 3, Steps: 2, Stages: 3, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

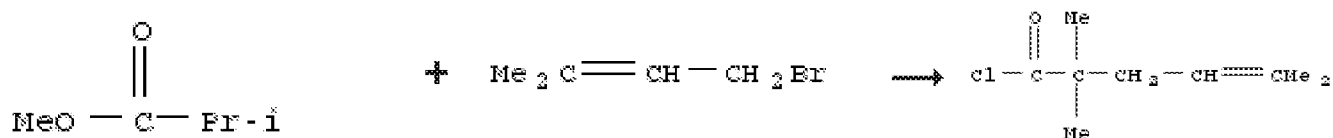
Step 1

2,2,5-Trimethyl-hex-4-enoyl chloride: methyl 2,2,5-trimethyl-hex-4-enoate (2.74 g, 16 mmol) was dissolved in ethanol (50 ml) and added to a solution of NaOH (3.0 g, 75 mmol) in water (35 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacua*. The residue was partitioned between pH 2 aqueous buffer (0.5 M NaHSO₄ / 0.5 M Na₂SO₄) and diethyl ether (3x150 ml). The combined organic layers were dried over Na₂CO₃ and the ether solvent removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoic acid (>95% pure) as a colourless oil. The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoyl chloride which was all used without purification in the next step. **2,2,5-Trimethyl-hex-4-enoyl chloride.**

Step 2

Example 23: (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactamhydro-pyrrolidine-5-carboxylate (4.11 g, 16 mmol) and Na₂CO₃ (5.09 g, 48 mmol) in water (50 ml) were added to a solution of 2,2,5-trimethyl-hex-4-enoyl chloride (16 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 50 ml). The combined organic layers were dried over Na₂CO₃ and reduced *in vacua*. The residue was purified by silica column chromatography (1:5 EtOAc: hexanes to EtOAc) to give (S)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam as a waxy solid (3.58 g, 84%). (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam, Yield (3.58 g, 84%). m.p. 43-44 °C; [α]_D²⁵ (c = 1, CHCl₃) +23.2; ν_{max}/cm⁻¹ 3394, 3251 (NH), 1674, 1633 (CO), 1503 (NH); δ_H (500 MHz, CDCl₃) 7.11 (1H, d, J 5.0, CHNH), 6.65-6.45 (1H, br m, CH₂NH), 5.04 (1H, t, J 7.5, CH=C), 4.44 (1H, ddd, J 11, 5.5, 1.5, CHNH), 3.24-3.16 (2H, m, CH₂NH), 2.20 (1H, dd, J 14.5, 7.5, C=CHCH₂), 2.15 (1H, dd, J 14.5, 7.5, C-CHCH₂), 2.03-1.90 (2H, m, 2 × ring CH), 1.84-1.72 (2H, m, 2 × ring CH), 1.65 (3H, s, CH₃), 1.56 (3H, s, CH₃), 1.45-1.28 (2H, m, 2 × ring CH), 1.13 (3H, s, CH₃) and 1.12 (3H, s, CH₃); δ_C (125 MHz, CDCl₃) 176.9, 176.0 (CO), 134.1, 119.9 (CH=CH), 52.1 (NHCHCO), 42.5 (CH₂CMe₂), 42.1 (CH₂N), 39.0, 31.5, 28.9, 28.0 (CH₂ lactam), 26.0, 25.0, 24.9, 17.9 (CH₃); m/z (MH⁺ C₁₅H₂₇N₂O₂ requires 267.2073) 267.2063.

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12. 2 Steps

Overview

Steps/Stages

- 1.1 R:LiN(Pr-i)₂, S:THF, 1 h, -78°C
- 1.2 14 h, -78°C → rt
- 2.1 R:NaOH, S:H₂O, S:EtOH, 6 h, reflux; cooled
- 2.2 R:Cl(O=)CC(=O)Cl, C:DMF, S:CH₂Cl₂, 1 h

Notes

1) reaction from p.37 in patent, 2) reaction from p.38 in patent, Reactants: 2, Reagents: 3, Catalysts: 1, Solvents: 4, Steps: 2, Stages: 4, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

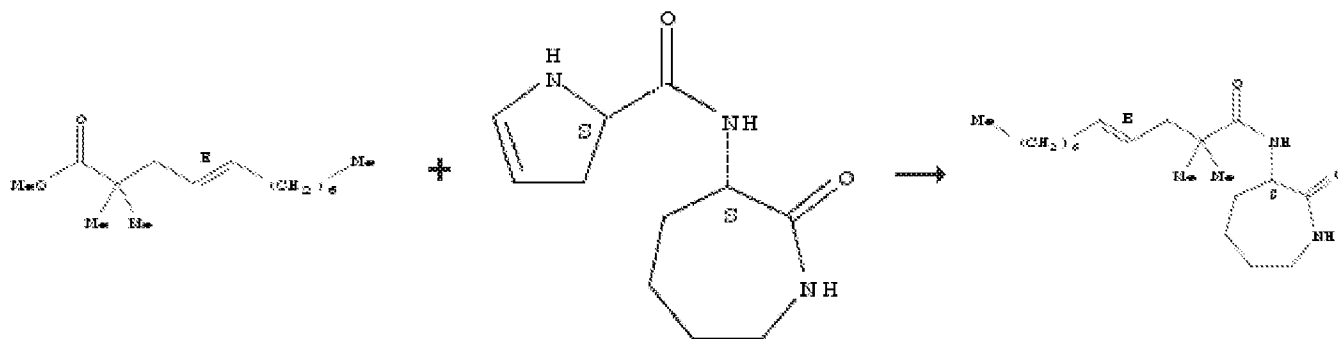
Step 1

Methyl 2,2,5-trimethyl-hex-4-enoate: butyllithium (2.9 M, 50 mmol) was added to a solution of diisopropylamine (7.2 ml, 50 mmol) in dry THF (200 ml) at -78 °C under N₂. The reaction was stirred at -78 °C for 20 minutes and then methyl isobutyrate (5.7 ml, 50 mmol) was added. The reaction was stirred at -78 °C for 1 hour, and then 3-methyl-but-2-enyl bromide (5.8 ml, 50 mmol) was added and the reaction was allowed to warm to ambient temperature over 14 hours. The reaction solvent was then removed in vacuo, and the residue was partitioned between pH 2 aqueous buffer (0.5 M NaHSO₄ / 0.5 M Na₂SO₄) and hexane (3 x 250 ml). The combined organic layers were dried over Na₂SO₄ and the hexane solvent removed in vacuo to give methyl 2,2,5-trimethyl-hex-4-enoate as a colourless oil (6.93 g 81%). Methyl 2,2,5-trimethyl-hex-4-enoate, Yield (6.93 g 81%). $\nu_{\text{max}}/\text{cm}^{-1}$ 1732 (CO); δ_{H} (400 MHz, CDCl₃) 5.04 (1H, tsept, J7.5, 1.5, CH=C), 3.63 (3H, s, OCH₃), 2.20 (2H, d, J7.5, CHCH₂), 1.68 (3H, br s, CH=CMeMe), 1.58 (3H, br s, CH=CMeMe), 1.14 (6H, s, (CH₃)₂CO); δ_{C} (125 MHz, CDCl₃) 178.4 (CO), 134.1 (Me₂OCH), 119.8 (Me₂C=CH), 51.6 (OCH₃), 42.8 (Me₂CCO), 38.7 (CH₂), 25.9, 24.7 (x 2), 17.8 (CCH₃); m/z (MH⁺ C₁₀H₁₉O₂ requires 171.1385) 171.1388.

Step 2

2,2,5-Trimiethyl-hex-4-enoyl chloride: methyl 2,2,5-trimethyl-hex-4-enoate (2.74 g, 16 mmol) was dissolved in ethanol (50 ml) and added to a solution of NaOH (3.0 g, 75 mmol) in water (35 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacua*. The residue was partitioned between pH 2 aqueous buffer (0.5 M NaHSO₄ / 0.5 M Na₂SO₄) and diethyl ether (3x150 ml). The combined organic layers were dried over Na₂CO₃ and the ether solvent removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoic acid (>95% pure) as a colourless oil. The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoyl chloride which was all used without purification in the next step. **2,2,5-Trimiethyl-hex-4-enoyl chloride.**

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13. 2 Steps

[Step 2.1]

Overview

Steps/Stages

- 1.1 R:NaOH, S:H₂O, S:EtOH, 6 h, reflux; cooled
- 1.2 R:Cl(O=)CC(=O)Cl, C:DMF, S:CH₂Cl₂, 1 h
- 2.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 12 h, rt

Notes

1) reaction from p.37 in patent, 2) reaction from p.29 in patent, Reactants: 2, Reagents: 3, Catalysts: 1, Solvents: 3, Steps: 2, Stages: 3, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

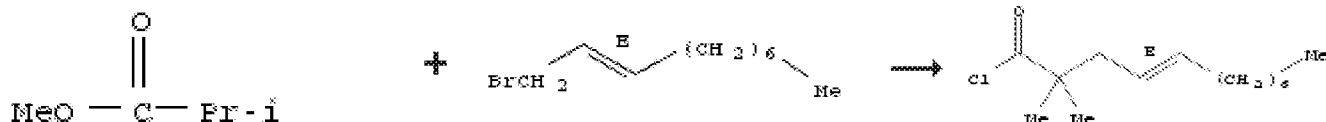
Step 1

(E)-2,2-Dimethyl-dodec-4-enoyl chloride: the entire product from the above reaction was then dissolved in ethanol (50 ml) and added to a solution of NaOH (2.0 g, 50 mmol) in water (25 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacuo*. The residue was partitioned between pH 2 aqueous buffer (0.5 M NaHSO₄ / 0.5 M Na₂SO₄) (100 ml) and diethyl ether (3 x 100 ml). The combined organic layers were dried over Na₂SO₄ and the ether solvent removed *in vacuo* to give crude (E)-2,2-dimethyl-dodec-4-enoic acid (>90% pure) as a colourless oil. The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacuo* to give crude (E)-2,2-dimethyl-dodec-4-enoyl chloride which was all used without purification in the next step. **(E)-2,2-Dimethyl-dodec-4-enoyl chloride**

Step 2

Example 22: (S,E)-3-(2',2'-Dimethyl-dodec-4'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (10 mmol) and Na₂CO₃ (3.0 mmol) in water (30 ml) were added to a solution of 2,2-dimethyl-dodec-2-enoyl chloride (crude, from above reaction) (10 mmol) in dichloromethane (30 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced *in vacuo*. The residue was purified by silica column chromatography (1:1 EtOAc: hexanes to EtOAc) to give (S,E)-3-(2',2'-dimethyl-dodec-4'-enoyl)amino-caprolactam as a colourless oil (2.12 g, 63%). (S,E)-3-(2',2'-Dimethyl-dodec-4'-enoyl)amino-caprolactam, Yield (2.12 g, 63%). [α]_D²⁵ (c = 1, CHCl₃ +21.6; ν_{max}/cm⁻¹ 3264 (NH), 1639 (CO), 1497 (NH); δ_H (500 MHz, CDCl₃) 7.09 (1H, d, J 5.5, CHNH), 6.67-6.32 (1H, br m, CH₂NH), 5.42 (1H, dt, J 15, 6.5, CH=CH), 5.28 (1H, dt, J 15, 7, CH=CH), 4.44 (1H, dd, J 11, 5.5, CHNH), 3.30-3.17 (2H, m, CH₂NH), 2.20 (1H, dd, 13.5, 7, CH=CHCH₂), 2.14 (1H, dd, 13.5, 7, CH=CHCH₂), 2.01-1.87 (4H, br m, ring CH x2, + CH₂CH=CH), 1.87-1.74 (2H, m, ring CH), 1.47-1.32 (2H, m, ring CH), 1.27-1.15 (10H, br m, (CH₂)₃ 1.1 3 (3H, s, CMeMe), 1.12 (3H, s, CMeMe) and 0.83 (3H, t, J7, CH₂CH₃); δ_C (125 MHz, CDCl₃) 176.8, 176.0 (CO), 134.2, 125.2 (CH=CH), 52.1 (NHCHCO), 43.9 (CH₂), 42.1 (x2)(CH₂+ CMe₂), 32.6, 31.8, 31.5, 30.1, 29.4, 29.1 (x2), 28.9, 27.9 (CH₂), 25.0, 24.8 (CH₃) and 22.6 (CH₃); m/z (MH⁺ C₂₀H₃₇N₂O₂ requires 337.2855) 337.2858.

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14. 2 Steps

Overview

Steps/Stages

- 1.1 R:LiN(Pr-i)₂, S:THF, 1 h, -78°C
- 1.2 14 h, -78°C → rt
- 2.1 R:NaOH, S:H₂O, S:EtOH, 6 h, reflux; cooled
- 2.2 R:Cl(O=)CC(=O)Cl, C:DMF, S:CH₂Cl₂, 1 h

Notes

1) reaction from p.36 in patent, 2) reaction from p.37 in patent, Reactants: 2, Reagents: 3, Catalysts: 1, Solvents: 4, Steps: 2, Stages: 4, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

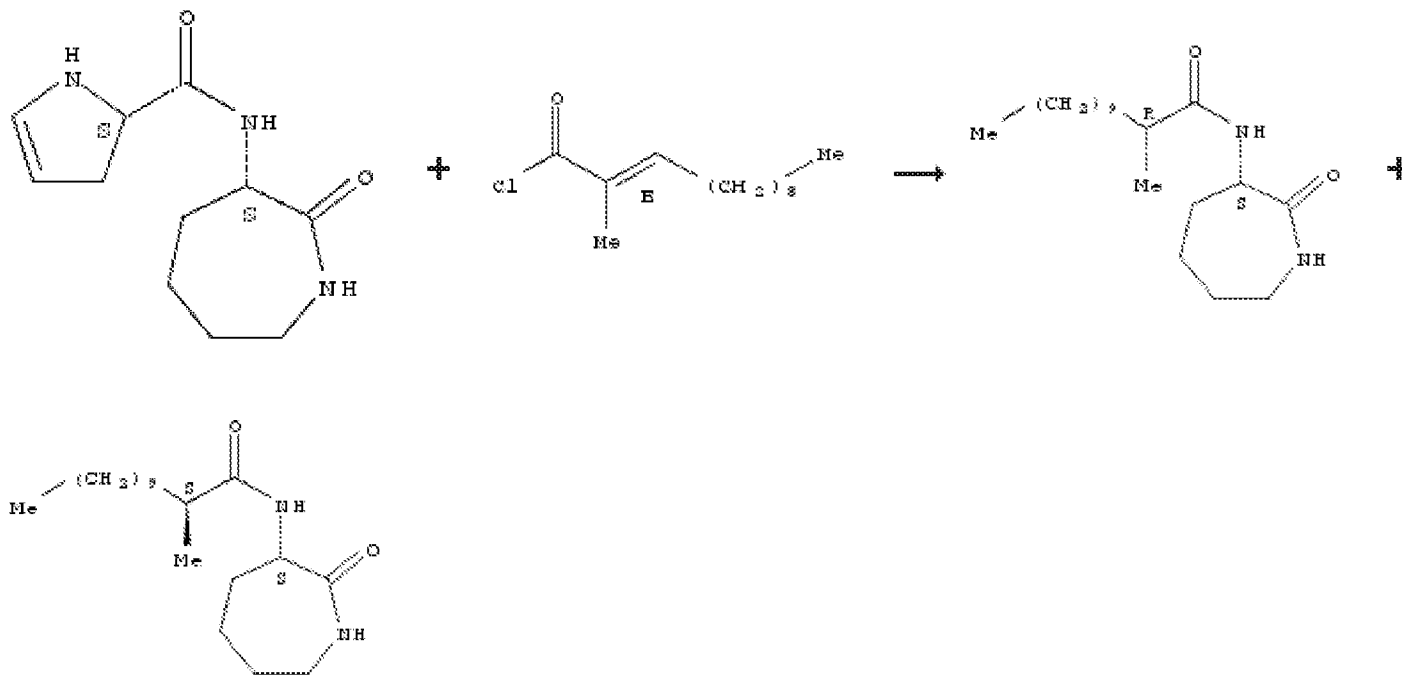
Step 1

(E)-Methyl 2,2-dimethyl-dodec-4-enoate: butyllithium (3.8 M, 10 mmol) was added to a solution of diisopropylamine (1.42 ml, 10 mmol) in dry THF at -78 °C under N₂. The reaction was stirred at -78 °C for 20 minutes and then methyl isobutyrate (1.15 ml, 10 mmol) was added. The reaction was stirred at -78 °C for 1 hour, and then (E)-dec-2-enyl bromide (2.19g, 10 mmol) was added and the reaction was allowed to warm to ambient temperature over 14 hours. The reaction solvent was then removed in vacuo, and the residue was partitioned between pH 2 aqueous buffer (0.5 M NaHSO₄ / 0.5 M Na₂SO₄) (100 ml) and hexane (3 x 100 ml). The combined organic layers were dried over Na₂SO₄ and the hexane solvent removed in vacuo to give crude (E)-methyl 2,2-dimethyl-dodec-4-enoate (>90% pure) (2.27 g) as a colourless oil (E)-Methyl 2,2-dimethyl-dodec-4-enoate, Yield (2.27 g). $\nu_{\text{max}}/\text{cm}^{-1}$ 1734 (CO); δ_{H} (400 MHz, CDCl₃) 5.42 (1H, br dt, J 15, 6.5, CH=CH), 5.30 (1H, dtt, J 15, 7, 1, CH=CH), 3.64 (3H, s, OCH₃), 2.18 (2H, dd, J 7, 1, CH₂CMe₂), 1.96 (2H, br q, J 6.5, CH₂CH₂CH=CH), 1.35-1.20 (10H, m, (CH₂)₈CH₃), 1.14 (6H, s, C(CH₃)₂), 0.87 (3H, t, J 6.5, CH₂CH₃) δ_{C} (125 MHz, CDCl₃) 178.2 (CO), 134.1, 125.2 (HC-CH), 51.5 (OCH₃), 43.6 (CH₂), 42.6 (Me₂CCO), 32.6, 31.8, 29.5, 29.1, 29.0 (CH₂), 24.7 (C(CH₃)₂), 22.6 (CH₂), 14.1 (CH₂CH₃); m/z (MH⁺ C₁₅H₂₉N₂O₂ requires 241.2168) 241.2169.

Step 2

(E)-2,2-Dimethyl-dodec-4-enoyl chloride: the entire product from the above reaction was then dissolved in ethanol (50 ml) and added to a solution of NaOH (2.0 g, 50 mmol) in water (25 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacuo*. The residue was partitioned between pH 2 aqueous buffer (0.5 M NaHSO₄ / 0.5 M Na₂SO₄) (100 ml) and diethyl ether (3 x 100 ml). The combined organic layers were dried over Na₂SO₄ and the ether solvent removed *in vacuo* to give crude (E)-2,2-dimethyl-dodec-4-enoic acid (>90% pure) as a colourless oil. The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacuo* to give crude (E)-2,2-dimethyl-dodec-4-enoyl chloride which was all used without purification in the next step. **(E)-2,2-Dimethyl-dodec-4-enoyl chloride**

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15. 2 Steps

Overview

Steps/Stages

Notes

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 12 h, rt

2.1 R:H₂, C: Pd(OH)₂, S: MeOH, 18 h, rt

1) reaction from p.42 in patent, 2) stereoselective, overall yield is greater than 95%, reaction from p.43 in patent, Reactants: 2, Reagents: 2, Catalysts: 1, Solvents: 3, Steps: 2, Stages: 2, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 15 Jun 2005

Experimental Procedure

Step 1

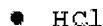
Example 49: (S)-(E)-3-(2'-Methyldodec-2'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (2 mmol) and Na₂CO₃ (6 mmol) in water (15 ml) were added to a solution of (E)-2-methyldodec-2-enoyl chloride (1.43 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacua. The residue was recrystallised from hexane to give (S)-(E)-3-(2'-methyldodec-2'-enoyl)amino-caprolactam (297 mg, 65%). (S)-(E)-3-(2'-Methyldodec-2'-enoyl)amino-caprolactam, Yield (297 mg, 65%). m.p. (hexanes) 99-100 °C; ν_{max}/cm⁻¹ 3282 (NH), 1656, 1622 (CO and C=C), 1497 (NH); [α]_D²⁵ (c = 1, CHCl₃) +38.2; ¹H (500 MHz, CDCl₃) 7.15 (1H, d, J 5.5, NHCH), 6.48-6.35 (2H, m, NHCH₂ + CH=C), 4.54 (1H, ddd, J 11, 5.5, 1.5, NHCH), 3.33-3.17 (2H, m, CHNH), 2.14-2.05 (3H, m, CH₂CH=C + lactam ring CH), 2.02-1.93 (1H, m, lactam ring CH), 1.88-1.77 (5H, m, lactam ring CH x2 + CH₃C=CH), 1.47-1.31 (4H, brm, lactam ring CH x2 + chain CH₂), 1.31-1.17 (12H, m, (CH₂)₆) and 0.85 (3H, t, J 7, CH₂CH₃); δ¹³C (125 MHz, CDCl₃) 175.9, 168.2 (CO), 136.9 (CH=C), 130.2 (CH=C), 52.3 (NHCH), 42.2 (NHCH₂), 31.8, 31.6, 29.5, 29.4 (x2), 29.3, 28.9, 28.7, 28.3, 27.9, 22.6 (CH₂), 14.1 and 12.4 (CH₃).

Step 2

Example 50(a): (3S,2'R) and Example 50(b): (3S',2'S)-3-(2-Methyldodecanoyl)amino-caprolactam: (S)-(E)-3-(2'-Methyldodec-2'-enoyl)amino-caprolactam (0.5 mmol) and Pd(OH)₂ (20% on carbon) were added to methanol (10 ml) and the mixture was stirred for 18 hours at ambient temperature under an atmosphere of hydrogen. The reaction was then filtered, and the solvent removed in vacuo to give (3S,2R) and (3S',2'S)-3-(2'-methyldodecanoyl)amino-caprolactam as a solid (160 mg, >95%). Example 50(a): (3S,2'R) and Example 50(b): (3S',2'S)-3-(2-Methyldodecanoyl)amino-caprolactam, Yield (160 mg, >95%). ν_{max}/cm⁻¹ 3313 (NH), 1671, 1636 (CO), 1515 (NH); δ¹H (500 MHz, CDCl₃) 6.91 (2H, d, J 5.5, CHNH, both isomers), 6.55 (2H, br s, CH₂NH, both isomers), 4.57-4.47 (2H, m, CHNH, both isomers), 3.34-3.18 (4H, m, CH₂NH, both isomers), 2.29-2.14 (2H, CH₃CHCO, both isomers), 2.07 (2H, br d, J 13.5, lactam ring CH, both isomers), 2.02-1.94 (2H, m, lactam ring CH, both isomers), 1.89-1.76 (4H, m, lactam ring CH x2, both isomers), 1.67-1.57 (2H, m, chain CH, both isomers), 1.51-1.33 (6H, m, lactam ring CH x2 + side chain CH₂, both isomers), 1.32-1.18 (32H, m, (CH₂)₈, both isomers), 1.13 (3H, d, J 7, CHCH₃, one isomer), 1.11 (3H, d, J 7, CHCH₃, one isomer) and 0.87 (6H, t, J 7.5, CH₃, both isomers); δ¹³C (125 MHz, CDCl₃) 175.9 (x2), 175.8 (x2) (CO, both isomers), 52.0, 51.9 (NCH), 42.1 (x2) (NCH₂, both isomers), 41.3, 41.2 (CHCH₃), 34.5, 34.1, 31.9 (x2), 31.8, 31.7, 29.6 (x6), 29.5 (x2), 29.3 (x2), 28.9 (x2), 28.0, 27.9, 27.4 (x2), 22.6 (x2) (CH₂) 17.8, 17.6 and 14.1 (x2) (CH₃); m/z (MH⁺ C₁₉H₃₇N₂O₂ requires 325.2855) 325.2858.

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16. 2 Steps



Steps/Stages

- 1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 4 h, rt
2.1 R:Na₂SO₃, S:H₂O, S:EtOH, 14 h, reflux; cooled

1) reaction from p.31 in patent, 2) reaction from p.32 in patent, Reactants: 2, Reagents: 2, Solvents: 3, Steps: 2, Stages: 2, Most stages in any one step: 1

Preparation of 3-aminocaprolactam
derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun
2005

Step 1

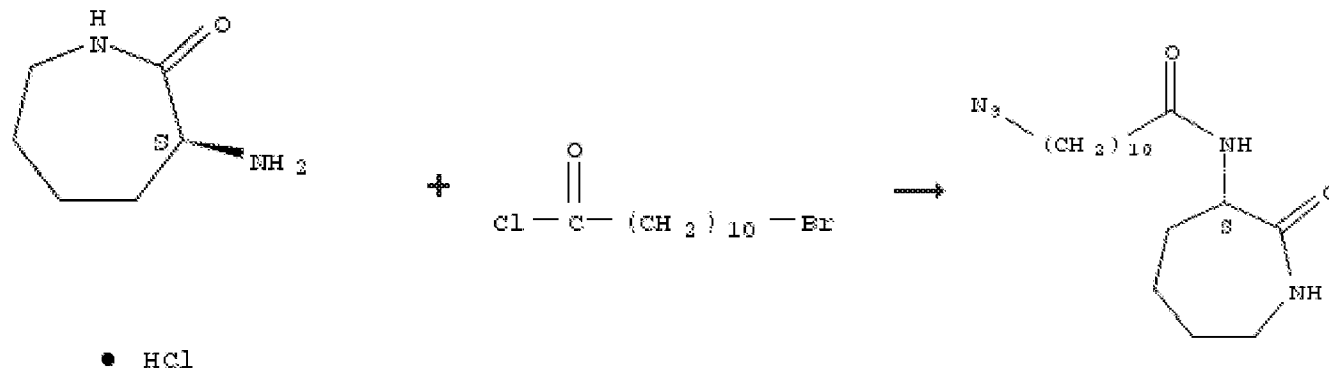
Example 25: (S)-3-(11'-bromo-undecanoyl)amino-caprolactam: (5)-3-amino-caprolactam hydrochloride (5 mmol) and Na₂CO₃ (15 mmol) in water (25 ml) were added to a solution of 11-bromo-undecanoyl chloride (5 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction was stirred for 4 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacua. The residue was purified by recrystallisation from EtOAc to give (S)-3-(11'-bromo-undecanoyl)amino-caprolactam (1.49 g, 79%). (S)-3-(11'-bromo-undecanoyl)amino-caprolactam, Yield (1.49 g, 79%). m.p. (EtOAc) 73-74 °C; [α]_D²⁵ (c = 1, CHCl₃) +31.8; ν_{max}/cm⁻¹ 3342, 3287 (NH), 1668, 1634 (CO), 1515 (NH); δ_H (500 MHz, d₆-DMSO) 7.76 (1H, t, J6.5, CH₂NH), 7.67 (1H, d, J7, CHNH), 4.38 (1H, dd, J11, 7, CHNH), 3.51 (2H, t, J6.5, CH₂Br), 3.15 (1H, ddd, J 15.5, 10.5, 5, CHNH), 3.05 (1H, dt, J14, 7, CHNH), 2.17-2.06 (2H, m, CH₂CONH), 1.85 (1H, dt, J14, 3, C-5 H), 1.82-1.68 (4H, m, C-4 H, C-6 H and CH₂CH₂Br), 1.62 (1H, qt, J12, 3.5, C-5 H), 1.46 (2H, br qn J6.5, CH₂CH₂CONH), 1.41-1.31 (3H, m, C-4 H and chain CH₂) and 1.31-1.13 (11H, m, (CH₂)₈ + C-6 H); δ_C (125 MHz, d₆-DMSO) 174.4 (CO-ring), 171.3 (CO-chain), 51.3 (NHCHCO), 40.7 (NCH₂), 35.3, 35.2, 32.4, 31.3, 29.0, 28.9 (x3), 28.7, 28.2, 27.8, 27.6 and 25.4 (CH₂); m/z (MH⁺ BrC₁₇H₃₂N₂O₂ requires 375.1647) 375.1655.

Step 2

Example 27: (S) Sodium 3-(undecanoyl)amino-caprolactam 11'-sulfonate tetrahydrate: sodium sulfite (630 mg, 5 mmol) in water (3 ml) was added to (1S)-3-(11-bromoundecanoyl) amino-caprolactam (375 mg, 1 mmol) in ethanol (2 ml) and the mixture was heated at reflux for 14 hours. The cooled reaction mixture was then added to ethanol (25 ml) and the reaction was filtered. The solvent was then removed in vacuo to give (S) Sodium 3-(undecanoyl)amino-caprolactam 11'-sulfonate tetrahydrate (456 mg, 97%) (S) Sodium 3-(undecanoyl)amino-caprolactam 11'-sulfonate tetrahydrate, Yield (456 mg, 97%), m.p. (EtOAc) 208-210 °C; $[\alpha]_D^{25}$ (c = 1, H₂O) -15.5; ν_{max} /cm⁻¹ 3430, 3344, 3289 (NH + H₂O), 1667, 1643 (C=O), 1530 (NH) 1195, 1183 (SO₃, asym.), 1064 (SO₃, sym.); δ H (500 MHz, d₆-DMSO) 7.76 (1H, t, J 6, CH₂NH), 7.70 (1H, d, J 7, CHNH), 4.35 (1H, dd, J 10, 7.5, CHNH), 3.42 (8H, s, 4 × H₂O) 3.17-3.00 (2H, m, CH₂NH), 2.47-2.38 (2H, m, CH₂SO₃), 2.17-2.05 (2H, m, CH₂CONH), 1.82 (1H, br s, J 13.5, C-5 H), 1.75-1.66 (2H, m, C-4 H, C-6 H), 1.65- 1.50 (3H, m, C-5 H + chain CH₂), 1.47-1.40 (2H, m, chain CH₂) 1.35 (1H, qd, J 13, 3, C-4 H), and 1.30-1.11 (13H, m, (CH₂)₉ + C-6 H); Sc (125 MHz, d₆-DMSO) 174.5 (CO-ring), 171.5 (CO-chain), 51.6 (CH₂SO₃), 51.4 (NHCHCO), 40.8 (NCH₂), 35.3, 31.3, 29.1 (×3), 29.0 (×2), 28.8, 28.6, 27.8, 25.5 and 25.1 (CH₂); m/z MNa+ C₁₇H₃₁N₂O₅SN₂ requires 421.1749) 421.1748.

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17. 2 Steps



Overview

Steps/Stages

- 1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 4 h, rt
 2.1 R:NaN₃, S:DMF, 14 h, 60°C

Notes

1) reaction from p.31 in patent, 2) reaction from p.31 in patent, Reactants: 2, Reagents: 2, Solvents: 3, Steps: 2, Stages: 2, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
 By Grainger, David John, Fox, David John
 From PCT Int. Appl., 2005053702, 15 Jun 2005

Experimental Procedure

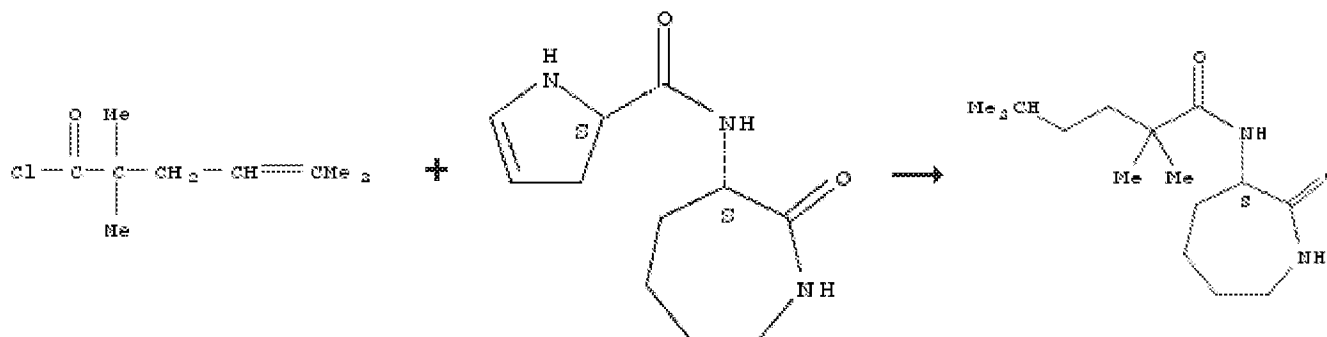
Step 1

Example 25: (S)-3-(11'-bromo-undecanoyl)amino-caprolactam: (S)-3-amino-caprolactam hydrochloride (5 mmol) and Na₂CO₃ (15 mmol) in water (25 ml) were added to a solution of 11-bromo-undecanoyl chloride (5 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction was stirred for 4 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacua. The residue was purified by recrystallisation from EtOAc to give (S)-3-(11'-bromo-undecanoyl)amino-caprolactam (1.49 g, 79%). (S)-3-(11'-bromo-undecanoyl)amino-caprolactam, Yield (1.49 g, 79%). m.p. (EtOAc) 73-74 °C; [α]_D²⁵ (c = 1, CHCl₃) +31.8; ν_{max} /cm⁻¹ 3342, 3287 (NH), 1668, 1634 (CO), 1515 (NH); δ H (500 MHz, d₆-DMSO) 7.76 (1H, t, J6.5, CH₂NH), 7.67 (1H, d, J 7, CHNH), 4.38 (1H, dd, J11, 7, CHNH), 3.51 (2H, t, J6.5, CH₂Br), 3.15 (1H, ddd, J 15.5, 10.5, 5, CHHNH), 3.05 (1H, dt, J14, 7, CHHNH), 2.17-2.06 (2H, m, CH₂CONH), 1.85 (1H, dt, J14, 3, C-5 H), 1.82-1.68 (4H, m, C-4 H, C-6 H and CH₂CH₂Br), 1.62 (1H, qt, J12, 3.5, C-5 H), 1.46 (2H, br qn J6.5, CH₂CH₂CONH), 1.41-1.31 (3H, m, C-4 H and chain CH₂) and 1.31-1.13 (11H, m, (CH₂)₈ + C-6 H); δ c (125 MHz, d₆-DMSO) 174.4 (CO-ring), 171.3 (CO-chain), 51.3 (NHCHCO), 40.7 (NCH₂), 35.3, 35.2, 32.4, 31.3, 29.0, 28.9 (x3), 28.7, 28.2, 27.8, 27.6 and 25.4 (CH₂); m/z (MH⁺ BrC₁₇H₃₂N₂O₂ requires 375.1647) 375.1655.

Step 2

Example 26: (S)-3-(11'-azido-undecanoyl)amino-caprolactam: Sodium azide (650 mg, 10 mmol) was added to (S)-3-(11-bromoundecanoyl) amino-caprolactam (375 mg, 1 mmol) in DMF (2 ml) and the mixture was heated at 60 °C for 14 hours. The solvent was then removed in vacuo and the residue was partitioned between water (20 ml) and EtOAc (3 x 20 ml). The combined organic layers were washed with 1M HCl aq (2 x 20 ml) and then dried over Na₂CO₃ and reduced in vacuo. The residue was purified by recrystallisation from EtOAc to give (S)-3-(11'-azido-undecanoyl)amino-caprolactam (221 mg, 66%). (S)-3-(11'-azido-undecanoyl)amino-caprolactam, Yield (221 mg, 66%). m.p. (EtOAc) 71-72 °C; [α]_D²⁵ (c= 1, CHCl₃) +34.7; ν_{max} /cm⁻¹ 3344, 3289 (NH), 2101 (N₃) 1668, 1631 (CO), 1516 (NH); δ H (500 MHz, d₆-DMSO) 7.77 (1H, t, J 6, CH₂NH), 7.67 (1H, d, J7, CHNH), 4.38 (1H, dd, J 11, 7, CHNH), 3.30 (2H, t, J 7, CH₂N₃), 3.15 (1H, ddd, J15.5, 10.5, 5, CHHNH), 3.05 (1H, dt, J14, 5.5, CHHNH), 2.17-2.07 (2H, m, CH₂CONH), 1.85 (1H, dt, J14, 3.5, C-5 H), 1.82-1.68 (2H, m, C-4 H, C-6 H), 1.62 (1H, qt, J 13, 3.5, C-5 H), 1.51 (4H, m, CH₂CH₂CONH and CH₂CH₂N₃), 1.36 (1H, qd, J13, 3, C-4 H), and 1.33-1.13 (13H, m, (CH₂)₆ + C-6 H); δ c (125 MHz, d₆-DMSO) 174.4 (CO-ring), 171.3 (CO-chain), 51.3 (NHCHCO), 50.7 (CH₂N₃), 40.7 (NCH₂), 35.3, 31.3, 29.0 (x2), 28.9, 28.7, 28.6, 28.3, 27.8, 26.2 and 25.4 (CH₂); m/z (MNa+ C₁₇H₃₁N₂O₂Na requires 360.2375) 360.2360.

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18. 2 Steps

Overview

Steps/Stages

- 1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 12 h, rt
- 2.1 R:H₂, C: Pd(OH)₂, S:AcOEt, 14 h, rt

Notes

1) reaction from p.30 in patent, 2) reaction from p.30 in patent, Reactants: 2, Reagents: 2, Catalysts: 1, Solvents: 3, Steps: 2, Stages: 2, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

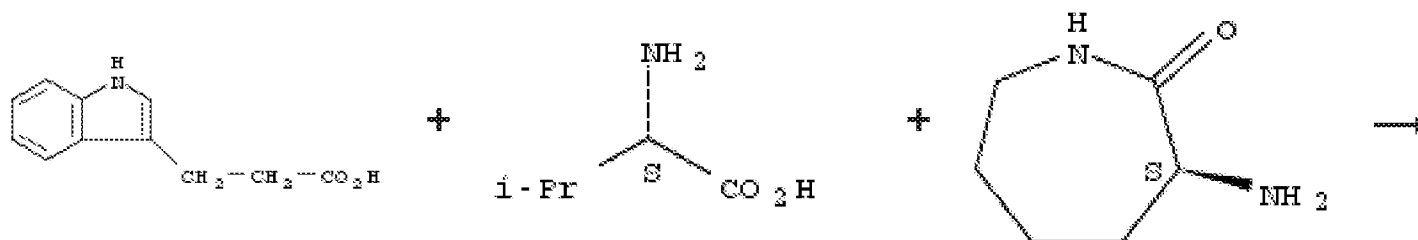
Step 1

Example 23: (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactamhydro-pyrrolidine-5-carboxylate (4.11 g, 16 mmol) and Na₂CO₃ (5.09 g, 48 mmol) in water (50 ml) were added to a solution of 2,2,5-trimethyl-hex-4-enoyl chloride (16 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 50 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacua. The residue was purified by silica column chromatography (1:5 EtOAc: hexanes to EtOAc) to give (S)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam as a waxy solid (3.58 g, 84%). (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam, Yield (3.58 g, 84%). m.p. 43-44 °C; [α]_D²⁵ (c = 1, CHCl₃) +23.2; ν_{max} /cm⁻¹ 3394, 3251 (NH), 1674, 1633 (CO), 1503 (NH); δ H (500 MHz, CDCl₃) 7.11 (1H, d, J 5.0, CHNH), 6.65-6.45 (1H, br m, CH₂NH), 5.04 (1H, t, J 7.5, CH=C), 4.44 (1H, ddd, J 11, 5.5, 1.5, CHNH), 3.24-3.16 (2H, m, CH₂NH), 2.20 (1H, dd, J 14.5, 7.5, C=CHCH₂), 2.15 (1H, dd, J 11, 5.5, 1.5, CHNH), 1.45-1.28 (2H, m, 2 x ring CH), 1.84-1.72 (2H, m, 2 x ring CH), 1.65 (3H, s, CH₃), 1.56 (3H, s, CH₃), 1.45-1.28 (2H, m, 2 x ring CH), 1.13 (3H, s, CH₃) and 1.12 (3H, s, CH₃); δ c (125 MHz, CDCl₃) 176.9, 176.0 (CO), 134.1, 119.9 (CH=CH), 52.1 (NHCHCO), 42.5 (CH₂CMe₂), 42.1 (CH₂N), 39.0, 31.5, 28.9, 28.0 (CH₂ lactam), 26.0, 25.0, 24.9, 17.9 (CH₃); m/z (MH⁺ C₁₅H₂₇N₂O₂ requires 267.2073) 267.2063.

Step 2

Example 24: (S)-3-(2',2',5'-Trimethyl-hexanoyl)amino-caprolactam: (S)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam (400 mg) was dissolved in EtOAc (25 ml), palladium hydroxide-on-carbon (20%, ca 100 mg) was added, and the mixture was stirred at ambient temperature under an atmosphere of hydrogen for 14 hours. The reaction was then filtered through a Celite® pad and the solvent was removed in vacua to give (S)-3-(2',2',5'-trimethyl-hexanoyl)aminocaprolactam as a waxy solid (400 mg, 98%). (S)-3-(2',2',5'-Trimethyl-hexanoyl)amino-caprolactam, Yield (400 mg, 98%). m.p. 73-74 °C; [α]_D²⁵ (c=1, CHCl₃) +27.8; ν_{max} /cm⁻¹ 3249 (NH), 1654, 1638 (CO), 1502 (NH); δ H (500 MHz, CDCl₃) 7.08 (1H, d, J 5.0, CHNH), 6.75-6.55 (1H, br m, CH₂NH), 4.44 (1H, ddd, J 11, 5.5, 1.5, CHNH), 3.29-3.16 (2H, m, CH₂NH), 2.03-1.91 (2H, m, 2 x ring CH), 1.84-1.73 (2H, m, 2 x ring CH), 1.47-1.28 (5H, m, 2 x ring CH + CH₂ + CH(CH₃)₂), 1.13 (3H, s, CH₃), 1.12 (3H, s, CH₃), 1.08-1.02 (2H, m, CH₂), 0.82 (3H, s, CH₃), 0.80 (3H, s, CH₃); δ c (125 MHz, CDCl₃) 177.1, 176.1 (CO), 52.1 (NHCHCO), 42.1 (CH₂N), 41.9 (CH₂CMe₂), 39.0, 33.7, 31.5, 28.9 (CH₂), 28.4 (Me₂CH), 27.9 (CH₂), 25.3, 25.2, 22.6, 22.5 (CH₃); m/z (MH⁺ C₁₅H₂₉N₂O₂ requires 269.2229) 269.2219.

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19. Single Step

96%

Overview

Steps/Stages

Notes

1) solid-supported reaction, solid-phase automated peptide synthesizer used, reaction from p.36 in patent, Reactants: 3, Steps: 1, Stages: 3, Most stages in any one step: 3

References

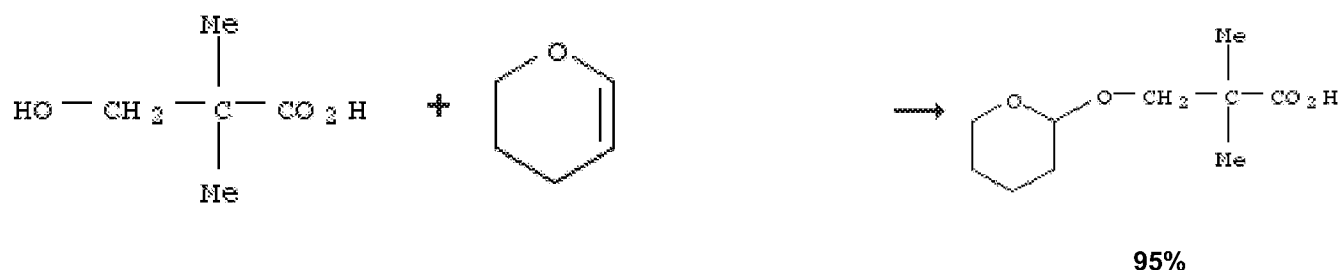
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 34: (S)-aminocaprolactam-(L)-valine-(TL)-Desaminotryptophan. This tripeptide was made on a solid-phase automated peptide synthesiser using (S)-aminocaprolactam for the final peptide coupling step. Mr(Calc) = 398.4600. Observed Mr by mass spectrometry 398.3. Purity (%TIC in molecular ion peak) = 96% **(S)-aminocaprolactam-(L)-valine-(TL)-Desaminotryptophan**

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20. Single Step



Overview

Steps/Stages

- 1.1 R:p-MeC₆H₄SO₃H, S:CH₂Cl₂, 3 h, rt
- 1.2 R:KOH, S:H₂O, S:EtOH, 18 h, reflux
- 1.3 S:H₂O, pH 2

Notes

1) regioselective in stage 1, Na₂SO₄/NaHSO₄ buffer used in stage 3, reaction from p.47 in patent, Reactants: 2, Reagents: 2, Solvents: 3, Steps: 1, Stages: 3, Most stages in any one step: 3

References

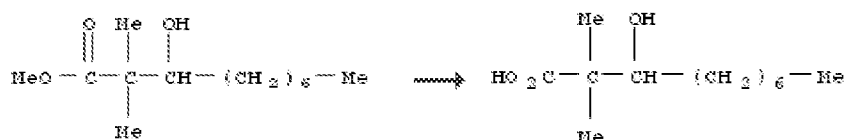
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 60: 2,2-Dimethyl-3-(tetrahydropyran-2-yloxy)-propionic acid (Intermediate) 2,2-Dimethyl-3-hydroxy propionic acid (100 mmol) and 3,4-dihydro-2H-pyran (210 mmol) were dissolved in dichloromethane (50 ml), and para-toluenesulfonic acid (10 mg) was added and the reaction was stirred at ambient temperature for 3 hours. The reaction solvent was then removed and the residue was dissolved in ethanol (100 ml). A solution of KOH (120 mmol) in water (30 ml) was added and the reaction was heated at reflux for 18 hours. The reaction solvent was removed in vacua and the residue was partitioned between water and diethyl ether. The aqueous layer was acidified with pH 2 buffer (0.5 M Na₂SO₄ / 0.5 M NaHSO₄) and then extracted with diethyl ether. The diethyl ether layer was then dried over Na₂SO₄ and the solvent was removed in vacuo to give 2,2-dimethyl-3-(tetrahydropyran-2-yloxy)-propionic acid as an oil (20.0 g, >95%). 2,2-Dimethyl-3-(tetrahydropyran-2-yloxy)-propionic acid, Yield (20.0 g, >95%). δ H (400 MHz, CDCl₃) 4.62 (1H, t, J 3.5, CHO₂), 3.82 (1H, ddd, J 12, 9, 3, ring CH₂O), 3.75 (1H, d, J 12, chain CH₂O), 3.55-3.46 (1H, m, ring CH₂O), 3.40 (1H, d, J 12, chain CH₂O), 1.90-1.45 (6H, m, (CH₂)₃), 1.25 (3H, s, CH₃) and 1.23 (3H, s, CH₃).

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21. Single Step



Overview

Steps/Stages

- 1.1 R:KOH, S:H₂O, S:EtOH, 18 h, reflux; cooled
- 1.2 S:H₂O, pH 2

Notes

1) Na₂SO₄/NaHSO₄ buffer used in stage 2, reaction from p.46 in patent, Reactants: 1, Reagents: 1, Solvents: 2, Steps: 1, Stages: 2, Most stages in any one step: 2

References

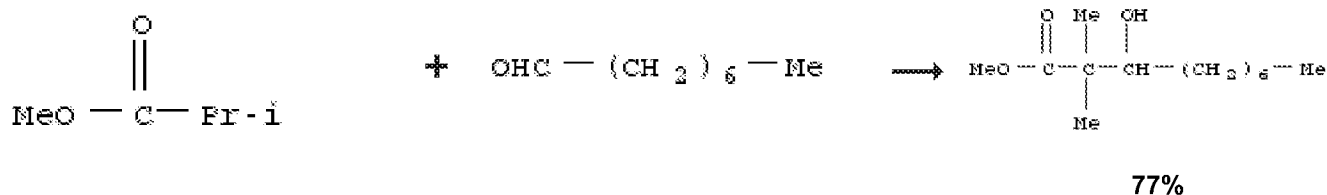
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053792, 16 Jun 2005

Experimental Procedure

Example 58: 2,2-Dimethyl-3-hydroxy decanoic acid (Intermediate). Methyl 2,2-dimethyl-3-hydroxy decanoate (20 mmol) was dissolved in EtOH (80 ml) and a solution of KOH (40 mmol) in water (20 ml) was added. The reaction was heated at reflux for 18 hours, and then the reaction was allowed to cool. The solvent was removed in vacuo and the residue was partitioned between water and diethyl ether. The aqueous layer was then acidified with pH 2 buffer (0.5 M Na₂SO₄ / 0.5 M NaHSO₄) and extracted with diethyl ether. The solution was dried over Na₂SO₄ and rediced in vacuo to give 2,2-dimethyl-3-hydroxy decanoic acid which solidified on standing 2,2-Dimethyl-3-hydroxy decanoic acid (Intermediate) m.p. 39-41 C; δ H (400 MHz, CDCl₃) 3.64 (1H, dd, J10, 2, CHOH), 1.67-1.12 (22H, m, (CH₂)₈ + C(CH₃)₂) and 0.88 (3H, t, J7, CH₂CH₃).

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22. Single Step



Overview

Steps/Stages

- 1.1 R:LiN(Pr-i)₂, S:THF, 45 min, -78°C
- 1.2 18 h, -78°C → rt
- 1.3 R:NH₄Cl, S:H₂O, rt

Notes

1) reaction from p.46 in patent, Reactants: 2, Reagents: 2, Solvents: 2, Steps: 1, Stages: 3, Most stages in any one step: 3

References

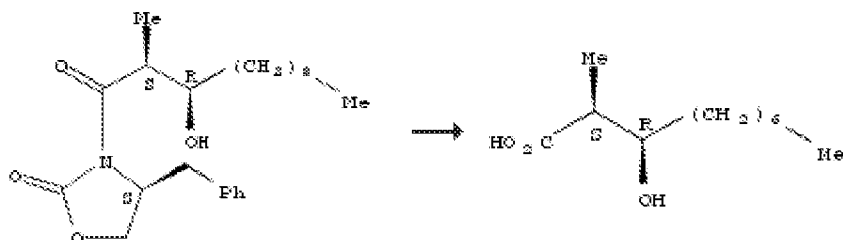
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 15 Jun 2005

Experimental Procedure

Example 57; Methyl 2,2-dimethyl-3-hydroxy decanoate (Intermediate), Butyllithium (2.5 M in hexanes, 50 mmol) was added to a solution of diisopropylamine (50 mmol) in dry THF (200 ml) at -78 °C under an atmosphere of dry nitrogen. The reaction was stirred for 30 minutes, and then methyl isobutyrate (50 mmol) was added. After 45 minutes, decanal (50 mmol) was added and the reaction was allowed to warm to ambient temperature over 18 hours. After the addition of saturated aqueous ammonium chloride (10 ml), the reaction solvent was removed in vacua and the residue was partitioned between hexanes and pH 2 buffer (0.5 M Na₂SO₄ / 0.5 M NaHSO₄). The organic layer was dried over Na₂SO₄ and the solvent was removed to give methyl 2,2-dimethyl-3-hydroxy decanoate as an oil (9.98g, 77%). Methyl 2,2-dimethyl-3-hydroxy decanoate (Intermediate), Yield (9.98g, 77%). δH (400 MHz, CDCl₃) 3.70 (3H, s, OCH₃), 3.69 (1H, dd, J10, 2, CHOH), 1.68-1.20 (16H, m, (CH₂)₈), 1.19 (3H, s, CCH₃), 1.17 (3H, s, CCH₃) and 0.88 (3H, t, J 7, CH₂CH₃) (no OH observed).

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23. Single Step



Overview

Steps/Stages

Notes

1.1 R:LiOH, R:H₂O₂, S:H₂O, S:THF, 18 h, rt

1.2 S:H₂O, rt, pH 2

1) Na₂SO₄/NaHSO₄ buffer used in stage 2, reaction from p.44 in patent, Reactants: 1, Reagents: 2, Solvents: 2, Steps: 1, Stages: 2, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

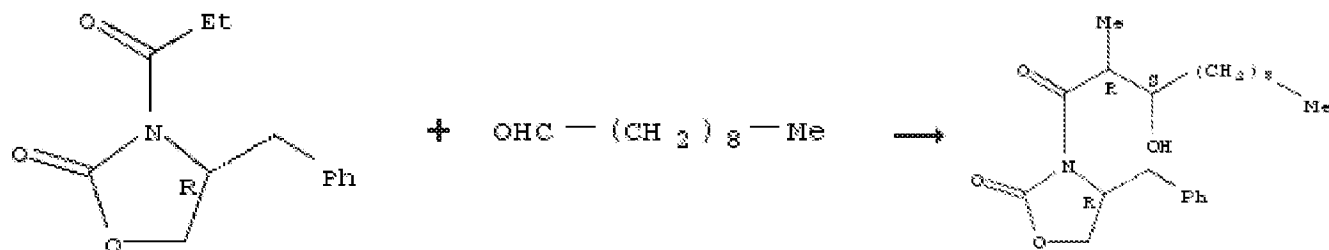
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 53: (2S,3R)-3-Hydroxy-2-methyldecanoic acid (Intermediate) (4S,2'S,3'R)-4-Benzyl-3-(3'-hydroxy-2'-methyldecanoyl)-oxazolidin-2-one (1.42 mmol) was dissolved in THF (10 ml). Water (2 ml), aqueous hydrogen peroxide (8M, 0.5 mmol) and LiOH.H₂O (3 mmol) were added, and the reaction was stirred for 18 hours. Na₂SO₃ (10 mmol) was added and the reaction was extracted with ethyl acetate. The aqueous layer was then acidified with pH 2 buffer (0.5 M Na₂SO₄/0.5 M NaHSO₄), and extracted with diethyl ether. The diethyl ether layer was dried over Na₂SO₄ and reduced in vacuo to give crude (2S,3R)-3-hydroxy-2-methyldecanoic acid; This material was used directly in the synthesis of (3S,2'S,3'R)-3-(3'-hydroxy-2'-methyldecanoyl)amino-caprolactam. (2S,3R)-3-Hydroxy-2-methyldecanoic acid (Intermediate) δ H (400 MHz, CDCl₃) 3.96-3.89 (1H, m, CHOH), 2.59 (1H, dq, J7, 3, CHCH₃), 1.54-1.36 (2H, m, CH₂), 1.36-1.22 (14H, m, (CH₃)₂) and 1.20 (3H, d, J7, CHCH₃).

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24. Single Step



Overview

Steps/Stages

1.1 R:TiCl₄, S:CH₂Cl₂, rt → -20°C; 15 min, -20°C

1.2 R:TiCl₄, 40 min

1.3 R:NMP, 10 min

1.4 1 h

Notes

1) stereoselective in stage 4, aldol reaction, reaction from p.44 in patent, Reactants: 2, Reagents: 2, Solvents: 1, Steps: 1, Stages: 4, Most stages in any one step: 4

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

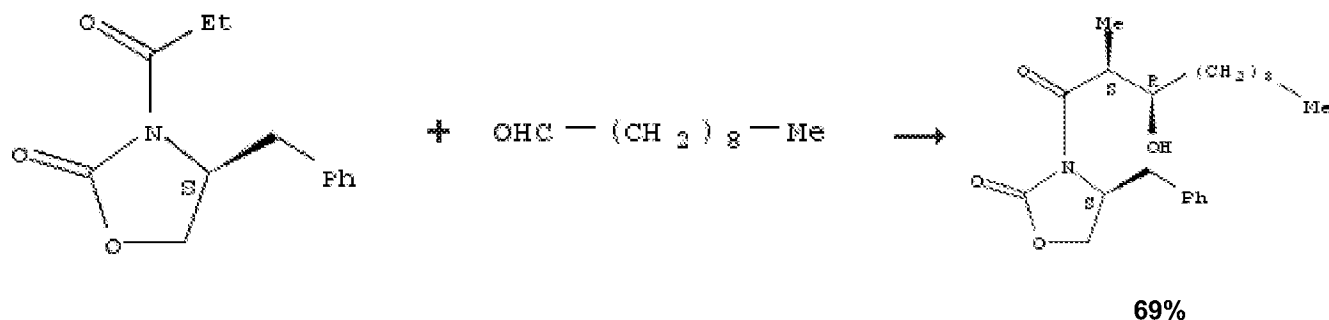
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

General/Typical Procedure: **Example 51: (4S,2'S,3'R)-4-Benzyl-3-(3'-hydroxy-2'-methyldecanoyl)-oxazolidin-2-one (Intermediate)** This aldol reaction was performed according to published method (Crimmins M.T; She, J.; Synlett, 2004, 1371-1374). (S)-4-Benzyl-3-propionyl-oxazolidin-2-one (5 mmol) (synthesised according to the method of Evans et al. Tetrahedron Lett., 1987, 28, 1123) was dissolved in CH₂Cl₂ (25 ml) and the solution was cooled to -20 °C under an atmosphere of dry nitrogen and TiCl₄ (5.25 mmol) was added. After 15 minutes, diisopropylethylamine (5.5 mmol) was added. After a further 40 minutes N-methyl-pyrrolidin-2-one (5.25 mmol) was added. After a further 10 minutes, decanal (5.5 mmol) was added and the reaction was stirred for 1 hour. Ammonium chloride solution was added and the reaction mixture was washed with pH 2 buffer (0.5 M Na₂SO₄ / 0.5 M NaHSO₄). The organic layer was dried over Na₂SO₄ and reduced in vacuo. The crude product was chromatographed on silica gel (10% to 33% ethyl acetate in hexane) to give (4S,2'S,3'R)-4-benzyl-3-(3'-hydroxy-2'-methyldecanoyl)-oxazolidin-2-one as an oil (1.34 g, 69%); **Example 52: (4R,2'R,3'S)-4-Benzyl-3-(3'-hydroxy-2'-methyldecanoyl)-oxazolidin-2-one (Intermediate)** (R)-4-Benzyl-3-propionyl-oxazolidin-2-one was converted into (4R,2'R,3'S)-4-benzyl-3-(3'-hydroxy-2'-methyldecanoyl)-oxazolidin-2-one according to the above procedure. NMR spectroscopic data is identical. m/z (MH⁺ C₂₃H₃₅NO₄ requires 390.2644) 390.2638.

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25. Single Step



Overview

Steps/Stages

- 1.1 R:TiCl₄, S:CH₂Cl₂, rt → -20°C; 15 min, -20°C
- 1.2 R:EtN(Pr-i)₂, 40 min
- 1.3 R:NMP, 10 min
- 1.4 1 h

Notes

1) stereoselective in stage 4, aldol reaction, reaction from p.43 in patent, Reactants: 2, Reagents: 3, Solvents: 1, Steps: 1, Stages: 4, Most stages in any one step: 4

References

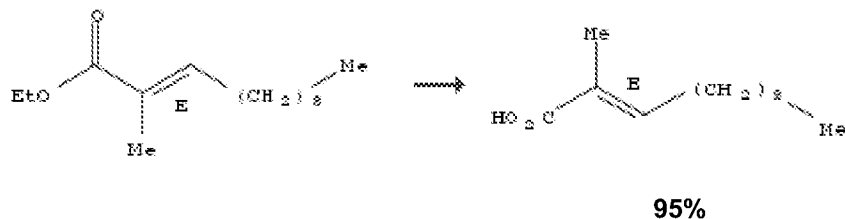
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 51: (4S,2'S,3'R)-4-Benzyl-3-(3'-hydroxy-2'-methyldecanoyl)-oxazolidin-2-one (Intermediate)
 This aldol reaction was performed according to published method (Crimmins M.T; She, J.; Synlett, 2004, 1371-1374). (S)-4-Benzyl-3-propionyl-oxazolidin-2-one (5 mmol) (synthesised according to the method of Evans et al. Tetrahedron Lett., 1987, 28, 1123) was dissolved in CH₂Cl₂ (25 ml) and the solution was cooled to -20 °C under an atmosphere of dry nitrogen and TiCl₄ (5.25 mmol) was added. After 15 minutes, diisopropylethylamine (5.5 mmol) was added. After a further 40 minutes N-methylpyrrolidin-2-one (5.25 mmol) was added. After a further 10 minutes, decanal (5.5 mmol) was added and the reaction was stirred for 1 hour. Ammonium chloride solution was added and the reaction mixture was washed with pH 2 buffer (0.5 M Na₂SO₄ / 0.5 M NaHSO₄). The organic layer was dried over Na₂SO₄ and reduced in vacuo. The crude product was chromatographed on silica gel (10% to 33% ethyl acetate in hexane) to give (4S,2'S,3'R)-4-benzyl-3-(3'-hydroxy-2'-methyldecanoyl)-oxazolidin-2-one as an oil (1.34 g, 69%); (4S,2'S,3'R)-4-benzyl-3-(3'-hydroxy-2'-methyldecanoyl)-oxazolidin-2-one, yield (1.34 g, 69%); $\nu_{\text{max}}/\text{cm}^{-1}$ 1778 (NCO₂), 1697 (CON); δ_{H} (500 MHz, CDCl₃) 7.35-7.30 (2H, m, meta-Ph), 7.29-7.24 (1H, m, para-Ph), 7.21-7.17 (2H, m, ortho-Ph), 4.69 (1H, ddt, J 9.5, 7.5, 3.5, CHN), 4.21 (1H, t, J 9, OCHH), 4.17 (1H, dd, J 9, 3, OCHH), 3.93 (1H, ddd, J 7, 4.5, 3, CHOH), 3.75 (1H, qd, J 7, 2.5, CHCH₃), 3.24 (1H, dd, J 13.5, 3.5, CHHPh), 2.87 (1H, br s, CHOH), 2.78 (1H, dd, J 13.5, 9.5, CHHPh), 1.56-1.20 (19H, m, (CH₂)₈ + CHCH₃) and 0.86 (3H, t, J 7, CH₂CH₃); δ_{C} (125 MHz, CDCl₃) 177.6 (CCO), 153.0 (OCO), 135.0 (ipso-Ph), 129.4, 129.0 (ortho- + meta- Ph), 127.4 (para- Ph), 71.5 (CHOH), 66.1 (OCH₂), 55.1 (NCH), 42.1 (CHCH₃), 37.8, 33.8, 31.9, 29.6 (x3), 29.3, 26.0, 22.7 (CH₂), 14.1 and 10.3 (CH₃); m/z (MH⁺ C₂₃H₃₆NO₄ requires 390.2644) 390.2641.

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26. Single Step



Overview

Steps/Stages

- 1.1 R:KOH, S:H₂O, S:EtOH, 18 h, reflux; cooled
- 1.2 R:HCl, S:H₂O, acidify

Notes

1) reaction from p.42 in patent, Reactants: 1, Reagents: 2, Solvents: 2, Steps: 1, Stages: 2, Most stages in any one step: 2

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
 By Grainger, David John, Fox, David John
 From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 47: (E)-2-Methyldodec-2-enoic acid (Intermediate). (E)-Ethyl 2-methyldodec-2-enoate (1.43 mmol) was dissolved in ethanol (10 ml), and KOH (10 mmol) in water (5 ml) was added. The reaction was heated at reflux for 18 hours and then cooled. The solvent was removed in vacuo and the residue partitioned between water and hexane. The aqueous layer was acidified with aqueous HCl, and was extracted with diethyl ether. The diethyl ether layer was dried over Na₂SO₄ and reduced in vacuo to give (E)-2-methyldodec-2-enoic acid as a solid (308 mg, >95%) (E)-2-Methyldodec-2-enoic acid (Intermediate), Yield (308 mg, >95%). m.p. 28-31 °C; δ_{H} (400 MHz, CDCl₃) 6.91 (1H, tq, 77.5, 1.5, CH=C), 2.18 (2H, br q, J 7.5, CH₂CH=C), 1.82 (3H, d, J 1.5, CH₃C=CH), 1.48-1.39 (2H, m, chain CH₂), 1.36-1.19 (12H, m, (CH₂)₆) and 0.88 (3H, t, J 7, (CH₂)₈CH₃) (no OH peak observed).

27. Single Step



Notes

1) stereoselective, reaction from p.41 in patent, Reactants: 2, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

Preparation of 3-aminocaprolactam
derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun
2005

Example 46: (E)-Ethyl 2-methyldodec-2-enoate (Intermediate). Decanal (5 mmol) and (carbethoxyethylidene)triphenylphosphorane (10 mmol) were dissolved in CH₂Cl₂ (20 ml) and the reaction was stirred for 18 hours. The solvent was then removed in vacua and the residue was filter through a plug of silica gel with the aid of 5% diethyl ether in hexanes. The collected eluent was reduced in vacua to give (E)-ethyl 2-methyldodec-2-enoate as an oil (1.02 g, 88%). (E)-Ethyl 2-methyldodec-2-enoate, Yield (1.02 g, 88%). $\nu_{\text{max}}/\text{cm}^{-1}$ 1709 (CO), 1651 (C=C); δ_{H} (500 MHz, CDCl₃) 6.73 (1H, tq, J 7.5, 1.5, CH=C), 4.16 (2H, q, J 7, OCH₂), 2.13 (2H, br q, J 7.5, CH₂CH=C), 1.80 (3H, d, J 1.5, CH₃C=CH), 1.45-1.37 (2H, m, chain CH₂), 1.32-1.19 (15H, m, (CH₂)₆ + OCH₂CH₃) and 0.85 (3H, t, J 7, (CH₂)₈CH₃); δ_{C} (125 MHz, CDCl₃) 168.3 (CO), 142.4 (CH=C), 127.6 (CH=C), 60.3 (OCH₂), 31.8, 29.5, 29.4 (x2), 29.3, 28.6, 28.5, 22.6 (CH₂), 14.3, 14.1 and 12.3 (CH₃); m/z (MH⁺ C₁₅H₂₉O₂ requires 241.2168) 241.2165.

28. Single Step



Notes

- 1.1 R:Me₃SiCl, R:Cul, S:THF, rt → -15°C; 1 h, -15°C; overnight, -15°C → rt
- 1.2 R:NH₄Cl, S:H₂O, rt
- 1.3 R:KOH, S:H₂O, S:EtOH, 18 h, reflux; cooled
- 1.4 R:HCl, S:H₂O, pH 2

1) reaction from p.40 in patent, Reactants: 2, Reagents: 5, Solvents: 3, Steps: 1, Stages: 4, Most stages in any one step: 4

References

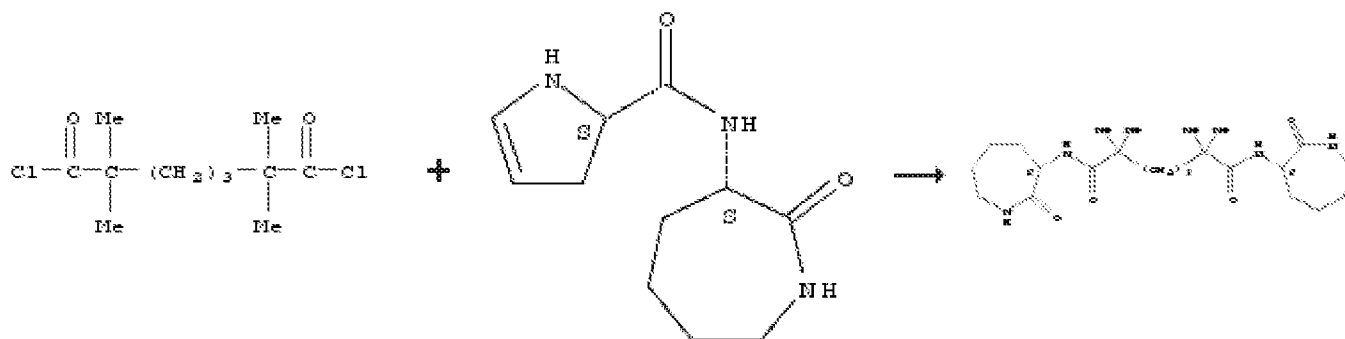
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 43: 3,3-Dimethyldodecanoic acid (Intermediate). Cul (2 mmol), trimethylsilyl chloride (24 mmol) and methyl 3,3-dimethylacrylate (20 mmol) in THF (25 mmol) was cooled to -15 °C, and a solution of nonylmagnesium bromide (24 mmol) in THF (80 ml) was added over one hour. The reaction was allowed to warm to room temperature overnight and it was then quenched by the addition of saturated aqueous ammonium chloride. The THF was removed in vacuo and the residue was partitioned between hexanes and water. The organic layer was reduced in vacuo and the crude methyl 3,3-dimethyldodecanoate was dissolved in ethanol (50 ml). KOH (100 mmol) in water (10 ml) was added and the reaction was heated at reflux for 18 hours. The reaction was then allowed to cool, and the solvent was removed in vacuo. and the residue was partitioned between hexane and water. The aqueous layer was then acidified to pH 2 with aqueous HCl. and extracted with diethyl ether. The ether layer was dried over Na₂SO₄ and the solution was then reduced in vacuo to give 3,3-dimethyldodecanoic acid as an oil (3.47 g, 76%). 3,3-Dimethyldodecanoic acid, Yield (3.47 g, 76%). $\nu_{\text{max}}/\text{cm}^{-1}$ 1702 (CO); δ_{H} (500 MHz, CDCl₃) 11.12 (1H, br s, OH), 2.21 (2H, s, CH₂CO); 1.32-1.20 (16H, m, (CH₂)₈), 1.00 (6H, s, C(CH₃)₂) and 0.87 (3H, t, J7, CH₂CH₃); δ_{C} (125 MHz, CDCl₃) 179.1 (CO), 45.9, 42.3 (CH₂), 33.2 (C(CH₃)₂), 31.9, 30.3, 29.6 (x2), 29.3, 27.1 (x2) (C(CH₃)₂), 24.0, 22.6 (CH₂) and 14.1 (CH₃); m/z (M⁺ C₁₄H₂₈O₂ requires 228.2089) 228.2082

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29. Single Step



46%

Overview

Steps/Stages

Notes

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 2 h, rt

1) reaction from p.38 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

(S,S) N,N'-bis-(2'-oxo-azepan-3'-yl) 2,2,6,6-tetramethylheptadiamide: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na₂CO₃ (6 mmol) in water (25 ml) were added to a solution of 2,2,6,6-tetramethyl-heptandioyl dichloride (1 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 × 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacuo. The residue was purified by recrystallisation from EtOAc to give (3,3)-dimer (199 mg, 46%). Yield 199 mg, 46% m.p. 234-236 °C; [α]_D²⁵ (c = 1, CHCl₃) +29.4; ν_{max} /cm⁻¹ 3379, 3255 (NH), 1683, 1637 (CO), 1507, 1497 (NH); δ H (500 MHz, CDCl₃) 7.07 (2H, d, J 5.5, CHNH), 6.42 (2H, br s, CH₂NH), 4.44 (2H, ddd, J₁₁, 5.5, 1.5, CHNH), 3.31-3.17 (4H, m, CH₂NH), 2.04-1.94 (4H, m, ring CH), 1.86-1.73 (4H, m, ring CH), 1.51-1.31 (8H, br m, 2 × ring CH + CH₂CMe₂) and 1.12 (14H, m, chain CH₂CH₂CH₂ + CMe₂); δ C (125 MHz, CDCl₃) 176.9, 175.9 (CO), 52.1 (NHCH), 42.0 (CMe₂), 42.1, 41.5, 31.5, 28.9, 28.0 (CH₂), 25.3, 25.1 (CH₃) and 20.0 (CH₂); m/z (M⁺ C₂₃H₄₀N₄O₄ requires 436.30496) 436.30437.

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30. Single Step



Overview

Steps/Stages

- 1.1 R:NaOH, S:H₂O, S:EtOH, 6 h, reflux; cooled
1.2 R:Cl(O=)CC(=O)Cl, C:DMF, S:CH₂Cl₂, 1 h

Notes

1) reaction from p.38 in patent, Reactants: 1, Reagents: 2, Catalysts: 1, Solvents: 3, Steps: 1, Stages: 2, Most stages in any one step: 2

References

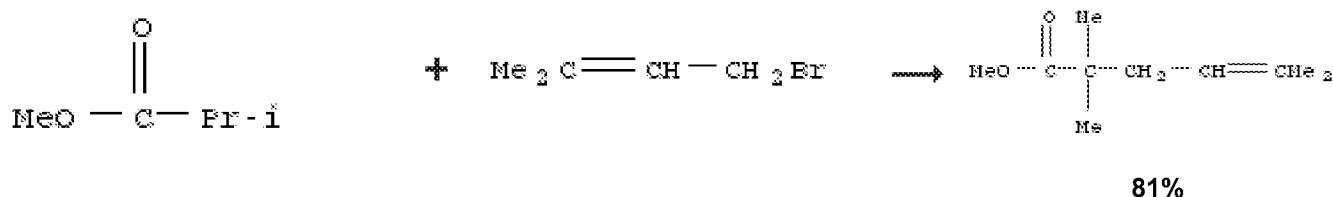
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

2,2,5-Trimethyl-hex-4-enoyl chloride: methyl 2,2,5-trimethyl-hex-4-enoate (2.74 g, 16 mmol) was dissolved in ethanol (50 ml) and added to a solution of NaOH (3.0 g, 75 mmol) in water (35 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacua*. The residue was partitioned between pH 2 aqueous buffer (0.5 M NaHSO₄ / 0.5 M Na₂SO₄) and diethyl ether (3x150 ml). The combined organic layers were dried over Na₂CO₃ and the ether solvent removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoic acid (>95% pure) as a colourless oil. The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacua* to give crude 2,2,5-trimethyl-hex-4-enoyl chloride which was all used without purification in the next step. **2,2,5-Trimethyl-hex-4-enoyl chloride.**

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31. Single Step



Overview

Steps/Stages

- 1.1 R:LiN(Pr-i)₂, S:THF, 1 h, -78°C
- 1.2 14 h, -78°C → rt

Notes

1) reaction from p.37 in patent, Reactants: 2, Reagents: 1, Solvents: 1, Steps: 1, Stages: 2, Most stages in any one step: 2

References

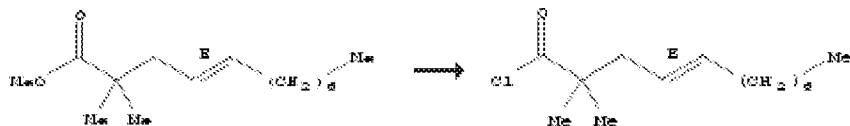
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 15 Jun 2005

Experimental Procedure

Methyl 2,2,5-trimethyl-hex-4-enoate: butyllithium (2.9 M, 50 mmol) was added to a solution of diisopropylamine (7.2 ml, 50 mmol) in dry THF (200 ml) at -78 °C under N₂. The reaction was stirred at -78 °C for 20 minutes and then methyl isobutyrate (5.7 ml, 50 mmol) was added. The reaction was stirred at -78 °C for 1 hour, and then 3-methyl-but-2-enyl bromide (5.8 ml, 50 mmol) was added and the reaction was allowed to warm to ambient temperature over 14 hours. The reaction solvent was then removed *in vacuo*, and the residue was partitioned between pH 2 aqueous buffer (0.5 M NaHSO₄ / 0.5 M Na₂SO₄) and hexane (3 x 250 ml). The combined organic layers were dried over Na₂SO₄ and the hexane solvent removed *in vacuo* to give methyl 2,2,5-trimethyl-hex-4-enoate as a colourless oil (6.93 g 81%). Methyl 2,2,5-trimethyl-hex-4-enoate, Yield (6.93 g 81%). $\nu_{\text{max}}/\text{cm}^{-1}$ 1732 (CO); δ_{H} (400 MHz, CDCl₃) 5.04 (1H, tsept, J7.5, 1.5, CH=C), 3.63 (3H, s, OCH₃), 2.20 (2H, d, J7.5, CHCH₂, 1.68 (3H, br s, CH=CMeMe), 1.58 (3H, br s, CH=CMeMe), 1.14 (6H, s, (CH₃)₂CO); δ_{C} (125 MHz, CDCl₃) 178.4 (CO), 134.1 (Me₂OCH), 119.8 (Me₂C=CH), 51.6 (OCH₃), 42.8 (Me₂CCO), 38.7 (CH₂), 25.9, 24.7 (x 2), 17.8 (CCH₃); m/z (MH⁺ C₁₀H₁₉O₂ requires 171.1385) 171.1388.

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32. Single Step



Overview

Steps/Stages

- 1.1 R:NaOH, S:H₂O, S:EtOH, 6 h, reflux; cooled
 1.2 R:Cl(O=)CC(=O)Cl, C:DMF, S:CH₂Cl₂, 1 h

Notes

1) reaction from p.37 in patent, Reactants: 1, Reagents: 2, Catalysts: 1, Solvents: 3, Steps: 1, Stages: 2, Most stages in any one step: 2

References

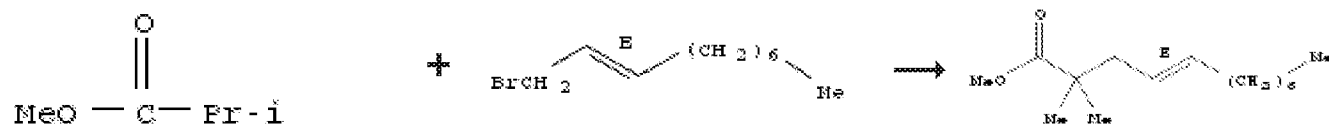
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
 By Grainger, David John, Fox, David John
 From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

(E)-2,2-Dimethyl-dodec-4-enoyl chloride: the entire product from the above reaction was then dissolved in ethanol (50 ml) and added to a solution of NaOH (2.0 g, 50 mmol) in water (25 ml). The mixture was heated at reflux for 6 hours, allowed to cool and the solvents were then removed *in vacuo*. The residue was partitioned between pH 2 aqueous buffer (0.5 M NaHSO₄ / 0.5 M Na₂SO₄) (100 ml) and diethyl ether (3 x 100 ml). The combined organic layers were dried over Na₂SO₄ and the ether solvent removed *in vacuo* to give crude (E)-2,2-dimethyl-dodec-4-enoic acid (>90% pure) as a colourless oil. The crude acid was dissolved in dichloromethane (50 ml) and oxalyl chloride (3 ml) was added along with a drop of DMF. The reaction was stirred for 1 hour and the solvent was removed *in vacuo* to give crude (E)-2,2-dimethyl-dodec-4-enoyl chloride which was all used without purification in the next step. **(E)-2,2-Dimethyl-dodec-4-enoyl chloride**

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33. Single Step



Overview

Steps/Stages

- 1.1 R:LiN(Pr-i)₂, S:THF, 1 h, -78°C
 1.2 14 h, -78°C → rt

Notes

1) reaction from p.36 in patent, Reactants: 2, Reagents: 1, Solvents: 1, Steps: 1, Stages: 2, Most stages in any one step: 2

References

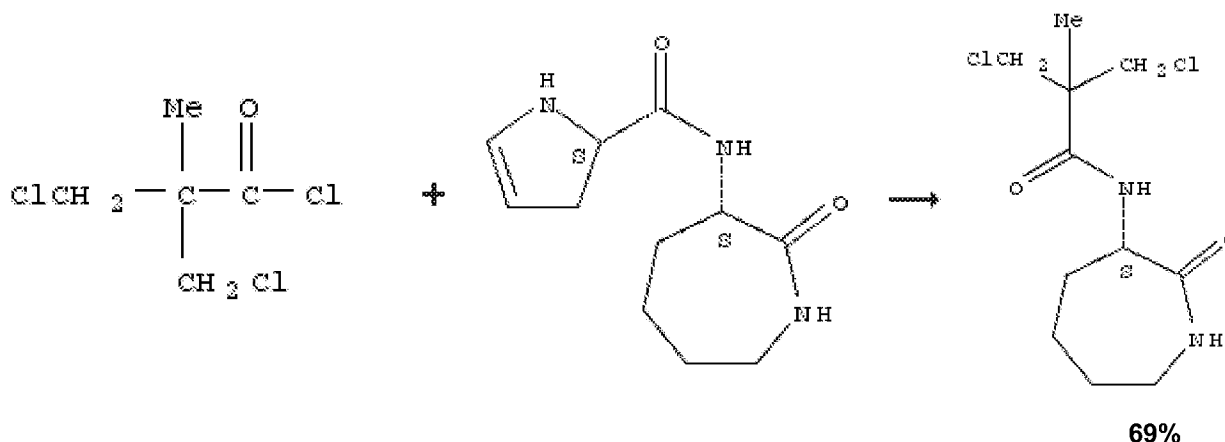
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
 By Grainger, David John, Fox, David John
 From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

(E)-Methyl 2,2-dimethyl-dodec-4-enoate: butyllithium (3.8 M, 10 mmol) was added to a solution of diisopropylamine (1.42 ml, 10 mmol) in dry THF at -78 °C under N₂. The reaction was stirred at -78 °C for 20 minutes and then methyl isobutyrate (1.15 ml, 10 mmol) was added. The reaction was stirred at -78 °C for 1 hour, and then (E)-dec-2-enyl bromide (2.19g, 10 mmol) was added and the reaction was allowed to warm to ambient temperature over 14 hours. The reaction solvent was then removed in vacuo, and the residue was partitioned between pH 2 aqueous buffer (0.5 M NaHSO₄ / 0.5 M Na₂SO₄) (100 ml) and hexane (3 x 100 ml). The combined organic layers were dried over Na₂SO₄ and the hexane solvent removed in vacuo to give crude (E)-methyl 2,2-dimethyl-dodec-4-enoate (>90% pure) (2.27 g) as a colourless oil (E)-Methyl 2,2-dimethyl-dodec-4-enoate, Yield (2.27 g). $\nu_{\text{max}}/\text{cm}^{-1}$ 1734 (CO); δ_{H} (400 MHz, CDCl₃) 5.42 (1H, br dt, J 15, 6.5, CH=CH), 5.30 (1H, dtt, J 15, 7, 1, CH=CH), 3.64 (3H, s, OCH₃), 2.18 (2H, dd, J 7, 1, CH₂CM₂), 1.96 (2H, br q, J 6.5, CH₂CH₂CH=CH), 1.35-1.20 (10H, m, (CH₂)₈CH₃), 1.14 (6H, s, C(CH₃)₂), 0.87 (3H, t, J 6.5, CH₂CH₃) δ_{C} (125 MHz, CDCl₃) 178.2 (CO), 134.1, 125.2 (HC-CH), 51.5 (OCH₃), 43.6 (CH₂), 42.6 (Me₂CCO), 32.6, 31.8, 29.5, 29.1, 29.0 (CH₂), 24.7 (C(CH₃)₂), 22.6 (CH₂), 14.1 (CH₂CH₃); m/z (MH⁺ C₁₅H₂₉N₂O₂ requires 241.2168) 241.2169.

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34. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 12 h, rt

Notes

1) reaction from p.48 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

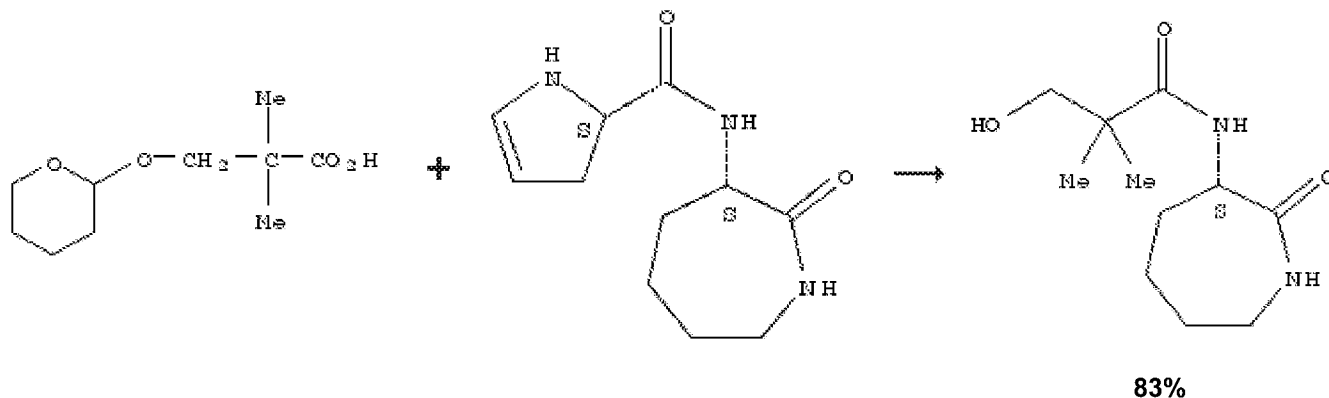
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 62: (S)-(3'-Chloro-2'-(chloromethyl)-2'-methylpropionyl)amino caprolactam. (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (5 mmol) and Na₂CO₃ (15 mmol) in water (15 ml) were added to a solution of 3,3'-dichloropivaloyl chloride (5 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂SO₄ and reduced in vacua. The residue was recrystallised from hexane to give (S)-(3'-chloro-2'-(chloromethyl)-2'-methylpropionyl)amino-caprolactam (973 mg, 69%). (S)-(3'-Chloro-2'-(chloromethyl)-2'-methylpropionyl)amino caprolactam. Yield (973 mg, 69%). m.p. (hexanes) 95-96 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ (c = 0.5, CHCl₃) +16.4; δ_{H} (500 MHz, CDCl₃) 7.33 (1H, d, J 5.0, CHNH), 6.82-6.62 (1H, br m, CH₂NH), 4.49 (1H, ddd, J₁₁, 5.5, 1.5, CHNH), 3.78 (1H, d, J₁₁, CHHCl), 3.74 (1H, d, J₁₁, CHHCl), 3.69 (1H, d, J₁₁, CHHCl), 3.66 (1H, d, J₁₁, CHHCl), 3.29-3.17 (2H, m, CH₂NH), 2.05 (1H, br s, J_{13.5}, ring CH), 2.01-1.93 (1H, m, ring CH), 1.87-1.71 (2H, m, 2 x ring CH) and 1.49-1.31 (3H, m, 2 x ring CH + CH₃); δ_{C} (125 MHz, CDCl₃) 175.4, 170.6 (CO), 52.6 (NHCHCO), 49.1 (CCO), 48.7, 48.6 (CH₂Cl), 42.1 (CH₂N), 31.1, 28.8, 27.9 (CH₂ lactam) and 18.9 (CH₃).

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35. Single Step



Overview

Steps/Stages

- 1.1 R:1-Benzotriazolol, R:Diimidazolylketone, S:THF, 4 h, reflux; reflux
→ rt
- 1.2 R:Disodiumcarbonate, S:H₂O, 18 h, rt
- 1.3 R:AcCl, S:MeOH, 18 h, rt

Notes

1) reaction from p.48 in patent, Reactants: 2, Reagents: 4, Solvents: 3, Steps: 1, Stages: 3, Most stages in any one step: 3

References

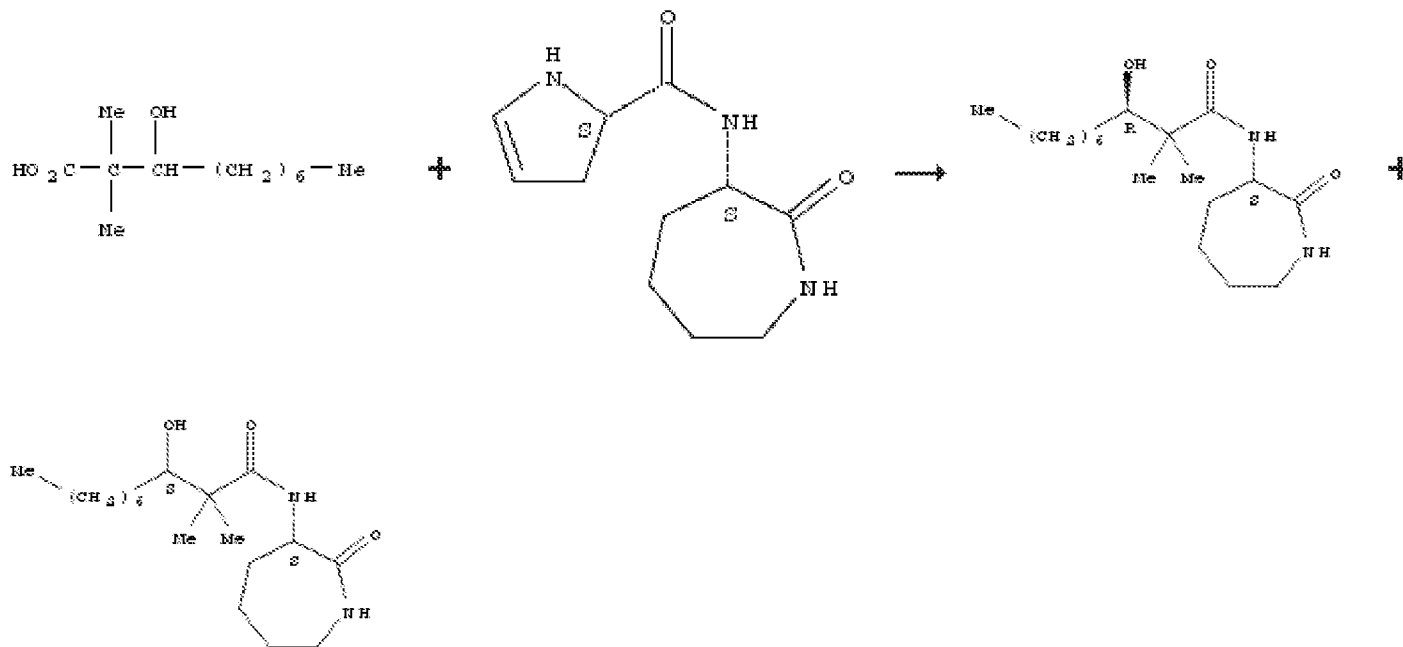
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 61: (S)-(2',2'-Dimethyl-3'-hydroxy-propionyl)amino-caprolactam 2,2-Dimethyl-3-(tetrahydropyran-2-yloxy)-propionic acid (4.65 mmol), 1-hydroxybenzotriazole monohydrate (4.65 mmol) and carbonyl diimidazole (4.50 mmol) were dissolved in THF (30 ml) and the reaction was heated at reflux for 4 hours. After the reaction was cooled to ambient temperature, a solution of (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (5 mmol) and Na₂CO₃ (15 mmol) in water (30 ml) was added and the reaction was stirred for 18 hours. The THF was then removed from the reaction by distillation in vacuo and the aqueous layer was extracted with ethyl acetate. The ethyl acetate layer was dried over Na₂SO₄ and reduced in vacuo. The residue was dissolved in MeOH, and acetyl chloride (1 ml) was added. The reaction was stirred at ambient temperature for 18 hours, and then reduced in vacuo to give (S)-(2'-dimethyl-3'-hydroxy propionyl)amino-caprolactam as a solid (854 mg, 83%). (S)-(2',2'-Dimethyl-3'-hydroxy-propionyl)amino-caprolactam, Yield (854 mg, 83%). m.p. 97-99 °C; [α]_D²⁵ (c = 0.5, CHCl₃) +30.0; δ_H (400 MHz, CDCl₃) 7.24 (1H, d, J 5.0, CHNH), 6.38 (1H, br s, CH₂NH), 4.49 (1H, dd, J 10, 6, CHNH), 3.54 (1H, d, J 11, CHHOH), 3.49 (1H, d, J 11, CHHOH), 3.33-3.20 (2H, m, CH₂NH), 2.03-1.96 (2H, m, 2 × ring CH), 1.87-1.72 (2H, m, 2 × ring CH), 1.50-1.30 (2H, m, 2 × ring CH), 1.20 (3H, s, CH₃) and 1.18 (3H, s, CH₃); δ_C (125 MHz, CDCl₃) 177.2, 176.0 (CO), 69.9 (CHOH), 52.1 (NHCHCO), 43.2 (CCO), 41.9 (CH₂N), 31.1, 28.8, 27.9 (CH₂ lactam), 22.4 and 22.3 (CH₃).

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36. Single Step



Overview

Steps/Stages

- 1.1 R:1-Benzotriazolol, R:EtN=C=N(CH₂)₃NMe₂·HCl, S:THF, 4 h, rt
- 1.2 R:Disodiumcarbonate, S:H₂O, 18 h, rt

Notes

1) stereoselective, combined yield = 88%, reaction from p.47 in patent, Reactants: 2, Reagents: 3, Solvents: 2, Steps: 1, Stages: 2, Most stages in any one step: 2

References

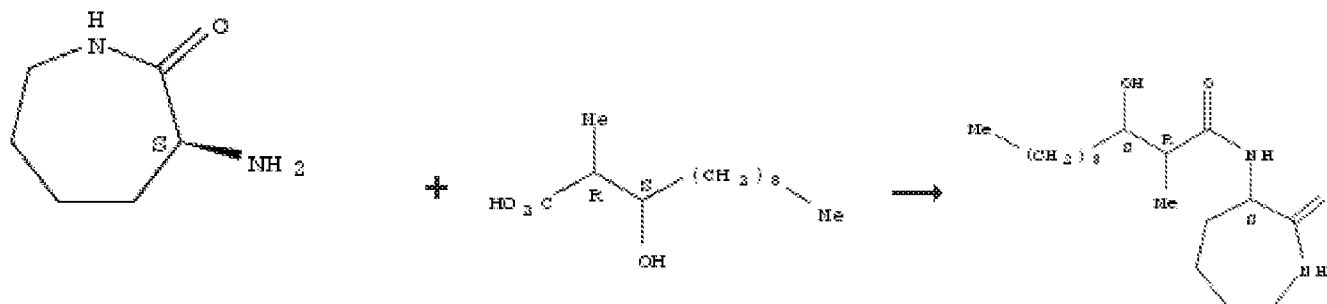
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 59(a): (3S,3'R) and Example 59(b): (3S,3'S)-3-(3'-Hydroxy-2',2'-dimethyldecanoyl)aminocaprolactam: 2,2-Dimethyl-3-hydroxy decanoic acid (1.77 mmol) and 1-hydroxybenzotriazole monohydrate (1.77 mmol) were dissolved in THF (10 ml). 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.77 mmol) was added and the reaction was stirred at ambient temperature for 4 hours. A solution of (S,S)-3- amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (2 mmol) and Na₂CO₃ (6 mmol) in water (15 ml) was added and the reaction was stirred for 18 hours. The reaction solvent was then removed in vacua and the residue was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with pH 2 buffer (0.5 M Na₂SO₄ / 0.5 M NaHSO₄ and dilute aqueous sodium hydroxide, and then dried over Na₂SO₄ and reduced in vacua. The residue was chromatographed on silica gel (25% ethyl acetate in hexanes to 100% ethyl acetate) to give a mixture of (3S,3R) and (3S,3'S)-3-(3'- hydroxy-2',2'-dimethyldecanoyl)amino-caprolactams (557 mg, 88%). Example 59(a): (3S,3'R) and Example 59(b): (3S,3'S)-3-(3'-Hydroxy-2',2'-dimethyldecanoyl)aminocaprolactam, Yield (557 mg, 88%). δ H (500 MHz, CDCl₃) 7.28 (1H, d, J 6, NHCH one isomer), 7.25 (1H, d, J6, NHCH, one isomer), 6.62-6.48 (1H, br m, NHCH₂, both isomers), 4.53-4.42 (1H, m, NCH, both isomers), 3.77 (1H, br d, J, 6, OH, one isomer), 3.63 (1H, br d, J, 6, OH, one isomer), 3.47-3.36 (1H, m, CHOH, both isomers), 3.32-3.17 (2H, m, NCH₂, both isomers), 2.07-1.92 (2H, m, lactam CH x2, both isomers), 1.87-1.71 (2H, m, lactam CH x2, both isomers), 1.60- 1.17 (21H, m, lactam CH x2 + chain (CH₂)₈ + CH₃, both isomers), 1.14 (3H, s, CCH₃, both isomers) and 0.84 (3H, t, J 7, CH₂CH₃, both isomers); δ c (125 MHz, CDCl₃) 177.6, 177.2, 175.8 (CO, both isomers), 77.8, 77.4 (CHOH), 52.1 (NCH, both isomers), 45.9, 45.8 (C(CH₃)₂), 42.1, 42.0 (NCH₂), 31.9 (x2) 31.6, 31.3, 30.9, 29.6 (*4), 29.3, 28.8, 27.9, 26.7, 26.6, 22.6 (CH₂), 23.7, 23.5, 21.1, 20.4 and 14.1 (CH₃).

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37. Single Step



• HCl

18%

Overview

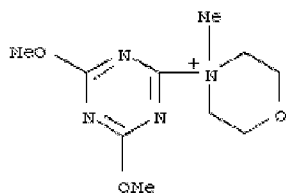
Steps/Stages

Notes

1.1 R:

S:MeOH, rt → 0°C; 4 h, 0°C

1) reaction from p.45 in patent, Reactants: 2,
Reagents: 2, Solvents: 1, Steps: 1, Stages: 1,
Most stages in any one step: 1

• Cl⁻R:Et₃N,**References**

Preparation of 3-aminocaprolactam
derivatives as anti-inflammatory agents

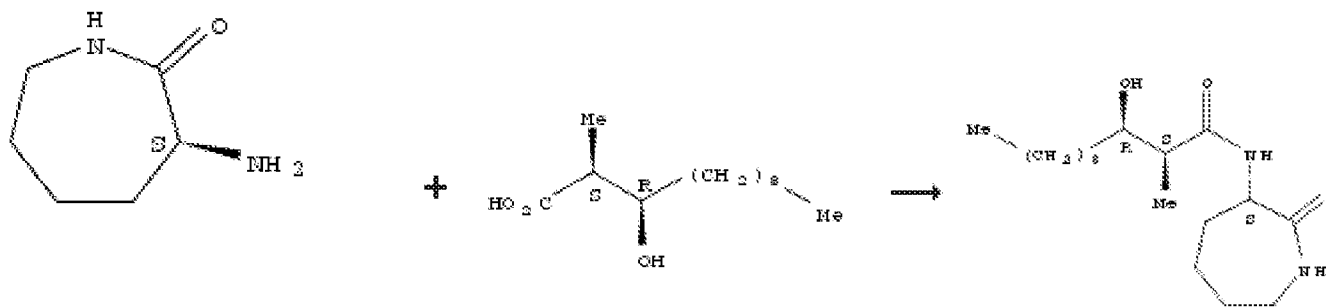
By Grainger, David John, Fox, David John

From PCT Int. Appl., 2005053702, 16 Jun
2005

Experimental Procedure

Example 56: (3S,2'R,3'S)-3-(3'-Hydroxy-2'-methyldecanoyl)amino-caprolactam: (2R,3'S)-3-Hydroxy-2-methyldecanoic acid (1.40 mmol), (S)-3-amino-caprolactam hydrochloride (1.50 mmol), triethylamine (2 mmol), and 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methyl-morpholinium chloride (1.40 mmol) were reacted together, as above to produce (3S,2'R,3'S)-3-(3'-hydroxy-2'-methyldecanoyl)amino-caprolactam which was recrystallised from ethyl acetate/hexane (86 mg, 18%). (3S,2'R,3'S)-3-(3'-Hydroxy-2'-methyldecanoyl)amino-caprolactam, Yield (86 mg, 18%). m.p. (hexanes) 118-121 °C; $\nu_{\text{max}}/\text{cm}^{-1}$, 3294 (NH), 1667, 1613 (CO), 1533 (NH); $[\alpha]_{\text{D}}^{25}$ (c = 0.5, CHCl₃) +14.8; δ_{H} (500 MHz, CDCl₃) 7.11 (1H, d, J₆, NHCH), 6.54 (1H, br s, NHCH₂), 4.53 (1H, ddd, J 11, 6.5, 1.5, NCH), 3.87-3.80 (1H, m, CHOH), 3.70 (1H, br s, OH), 3.34-3.20 (2H, m, NCH₂), 2.37 (1H, dq, J 7, 3, CHCH₃), 2.11-1.96 (2H, m, lactam CH ×2), 1.90-1.76 (2H, m, lactam CH ×2), 1.55-1.21 (18H, m, lactam CH ×2+ chain (CH₂)₃), 1.16 (3H, d, J 7, CHCH₃) and 0.88 (3H, t, J₇, CH₂CH₃); δ_{C} (125 MHz, CDCl₃) 175.9, 175.7 (CO), 72.0 (CHOH), 52.1 (NCH), 44.8 (CHCH₃), 42.1 (NCH₂), 33.7, 31.9, 31.4, 29.6 (×2), 29.5, 29.3, 28.8, 27.9, 26.0, 22.7 (CH₂), 14.1 and 10.7 (CH₃); m/z (MH⁺ C₁₉H₃₇N₂O₃ requires 341.2804) 341.2803.

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38. Single Step

• HCl

72%

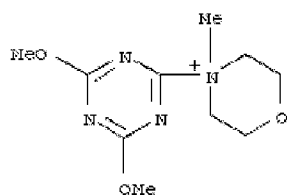
Overview

Steps/Stages**Notes**

1.1 R:

S:MeOH, rt → 0°C; 4 h, 0°C

1) reaction from p.45 in patent, Reactants: 2,
Reagents: 2, Solvents: 1, Steps: 1, Stages: 1,
Most stages in any one step: 1

• Cl⁻R:Et₃N,

References

Preparation of 3-aminocaprolactam
derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

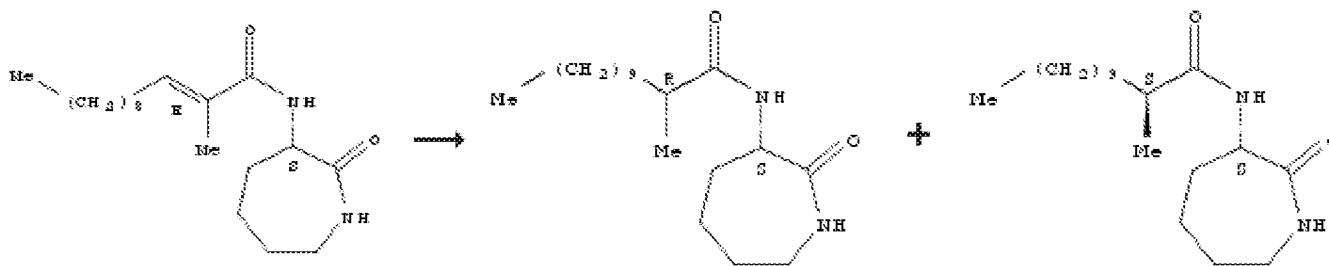
From PCT Int. Appl., 2005053702, 16 Jun
2005

Experimental Procedure

Example 55: (3S,2'S,3'R)-3-(3-Hydroxy-2'-methyldecanoyl)amino-caprolactam: (2S,3R)-3-Hydroxy-2-methyldecanoic acid (1.40 mmol) was dissolved in MeOH (10 ml), and (S)-3-amino-caprolactam hydrochloride (1.50 mmol) and triethylamine (2 mmol) were added. The reaction was cooled to 0 °C and 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methyl-morpholinium chloride (1.40 mmol) was added. The reaction was stirred for 4 hours, and then the solvent was removed in vacuo. The residue was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with dilute aqueous HCl and dilute aqueous NaOH, and then dried over Na₂SO₄. The solvent was removed in vacuo and the residue was recrystallised from ethyl acetate / hexane to give (3S,2'S,3'R)-3-(3'-hydroxy-2'-methyldecanoyl)amino-caprolactam as a solid (341 mg, 72%) (3S,2'S,3'R)-3-(3-Hydroxy-2'-methyldecanoyl)amino-caprolactam, Yield (341 mg, 72%). m.p.(hexanes) 88-91 °C; ν_{max}/cm⁻¹ 3313 (NH), 1628 (CO), 1480 (NH); [α]_D²⁵ (c = 0.5, CHCl₃) +40.8; δ_H (500 MHz, CDCl₃) 7.08 (1H, d J 5.5, NHCH), 6.51 (1H, br s, NHCH₂), 4.57 (1H, ddd, J 11, 6.5, 1, NCH), 3.83 (1H, dt, J 8, 4, CHOH), 3.36-3.21 (2H, m, NCH₂), 2.40 (1H, dq, J 7, 3, CHCH₃), 2.12-1.96 (2H, m, lactam CH × 2), 1.90-1.76 (2H, m, lactam CH × 2), 1.55-1.34 (4H, m, lactam CH × 2 + chain CH₂), 1.34-1.21 (14H, m, (CH₂)), 1.17 (3H, d, J 7, CHCH₃) and 0.88 (3H, t, J 7, CH₂CH₃) (OH not observed); δ_C (125 MHz, CDCl₃) 175.8, 175.7 (CO), 72.1 (CHOH), 52.0 (NCH), 44.6 (CHCH₃), 42.1 (NCH₂), 33.4, 31.9, 31.3, 29.6 (x2), 29.5, 29.3, 28.8, 27.9, 26.1, 22.7 (CH₂), 14.1 and 11.2 (CH₃); m/z (MH⁺ C₁₉H₃₇N₂O₃ requires 341.2804) 341.2776.

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39. Single Step



Overview

Steps/Stages

Notes

1.1 R:H₂, C:Pd(OH)₂, S:MeOH, 18 h, rt

1) stereoselective, overall yield is greater than 95%, reaction from p.43 in patent, Reactants: 1, Reagents: 1, Catalysts: 1, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

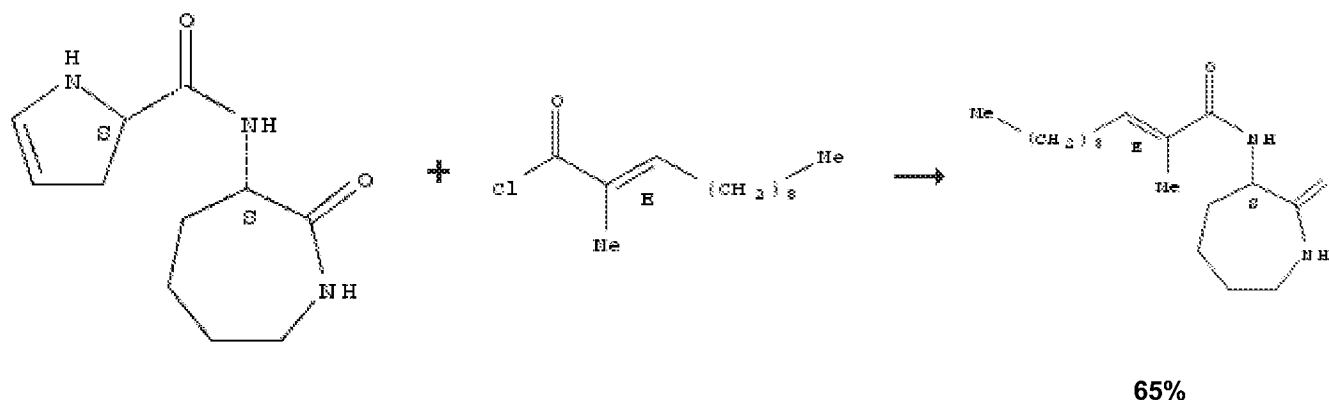
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 50(a): (3S,2'R) and Example 50(b): (3S',2'S)-3-(2-Methyldodecanoyl)amino-caprolactam: (5)-(E)-3-(2'-Methyldodec-2'-enoyl)amino-caprolactam (0.5 mmol) and Pd(OH)₂ (20% on carbon) were added to methanol (10 ml) and the mixture was stirred for 18 hours at ambient temperature under an atmosphere of hydrogen. The reaction was then filtered, and the solvent removed in vacuo to give (3S,2R) and (3S',2'S)-3-(2'-methyldodecanoyl)amino-caprolactam as a solid (160 mg, >95%). Example 50(a): (3S,2'R) and Example 50(b): (3S',2'S)-3-(2-Methyldodecanoyl)amino-caprolactam, Yield (160 mg, >95%). $\nu_{\text{max}}/\text{cm}^{-1}$ 3313 (NH), 1671, 1636 (CO), 1515 (NH); δ_{H} (500 MHz, CDCl₃) 6.91 (2H, d, J 5.5, CHNH, both isomers), 6.55 (2H, br s, CH₂NH, both isomers), 4.57-4.47 (2H, m, CHNH, both isomers), 3.34-3.18 (4H, m, CH₂NH, both isomers), 2.29-2.14 (2H, CH₃CHCO, both isomers), 2.07 (2H, br d, J13.5, lactam ring CH, both isomers), 2.02-1.94 (2H, m, lactam ring CH, both isomers), 1.89-1.76 (4H, m, lactam ring CH x2, both isomers), 1.67-1.57 (2H, m, chain CH, both isomers), 1.51-1.33 (6H, m, lactam ring CH x2 + side chain CH₂, both isomers), 1.32-1.18 (32H, m, (CH₂)₈, both isomers), 1.13 (3H, d, J 7, CHCH₃, one isomer), 1.11 (3H, d, J7, CHCH₃, one isomer) and 0.87 (6H, t, J7.5, CH₃, both isomers); δ_{C} (125 MHz, CDCl₃) 175.9 (x2), 175.8 (x2) (CO, both isomers), 52.0, 51.9 (NCH), 42.1 (x2) (NCH₂, both isomers), 41.3, 41.2 (CHCH₃), 34.5, 34.1, 31.9 (x2), 31.8, 31.7, 29.6 (x6), 29.5 (x2), 29.3 (x2), 28.9 (x2), 28.0, 27.9, 27.4 (x2), 22.6 (x2) (CH₂) 17.8, 17.6 and 14.1 (x2) (CH₃); m/z (MH⁺ C₁₉H₃₇N₂O₂ requires 325.2855) 325.2858.

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40. Single Step



Overview

Steps/Stages

Notes

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 12 h, rt

1) reaction from p.42 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

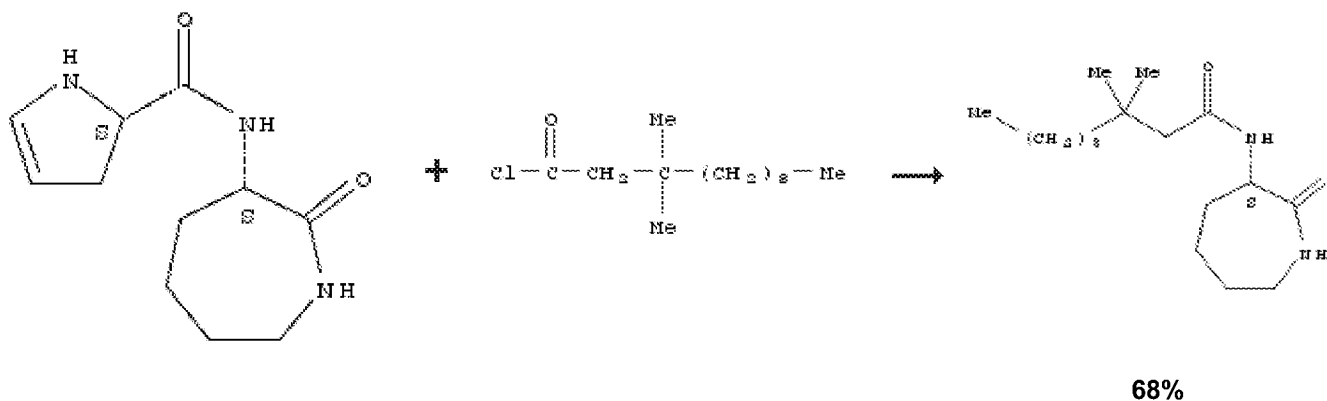
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 49: (S)-(E)-3-(2'-Methyldodec-2'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (2 mmol) and Na₂CO₃ (6 mmol) in water (15 ml) were added to a solution of (E)-2-methyldodec-2-enoyl chloride (1.43 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacua. The residue was recrystallised from hexane to give (S)-(E)-3-(2'-methyldodec-2'-enoyl)amino-caprolactam (297 mg, 65%). (S)-(E)-3-(2'-Methyldodec-2'-enoyl)amino-caprolactam, Yield (297 mg, 65%). m.p. (hexanes) 99-100 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ 3282 (NH), 1656, 1622 (CO and C=C), 1497 (NH); $[\alpha]_{\text{D}}^{25}$ (c = 1, CHCl₃) +38.2; ¹H (500 MHz, CDCl₃) 7.15 (1H, d, J5.5, NHCH), 6.48-6.35 (2H, m, NHCH₂ + CH=C), 4.54 (1H, ddd, J11, 5.5, 1.5, NHCH), 3.33-3.17 (2H, m, CHNH), 2.14-2.05 (3H, m, CH₂CH=C + lactam ring CH), 2.02-1.93 (1H, m, lactam ring CH), 1.88-1.77 (5H, m, lactam ring CH x2 + CH₃C=CH), 1.47-1.31 (4H, brm, lactam ring CH x2 + chain CH₂), 1.31-1.17 (12H, m, (CH₂)₆) and 0.85 (3H, t, J7, CH₂CH₃); ¹³C (125 MHz, CDCl₃) 175.9, 168.2 (CO), 136.9 (CH=C), 130.2 (CH=C), 52.3 (NHCH), 42.2 (NHCH₂), 31.8, 31.6, 29.5, 29.4 (x2), 29.3, 28.9, 28.7, 28.3, 27.9, 22.6 (CH₂), 14.1 and 12.4 (CH₃).

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41. Single Step



Overview

Steps/Stages

Notes

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 12 h, rt

1) reaction from p.41 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

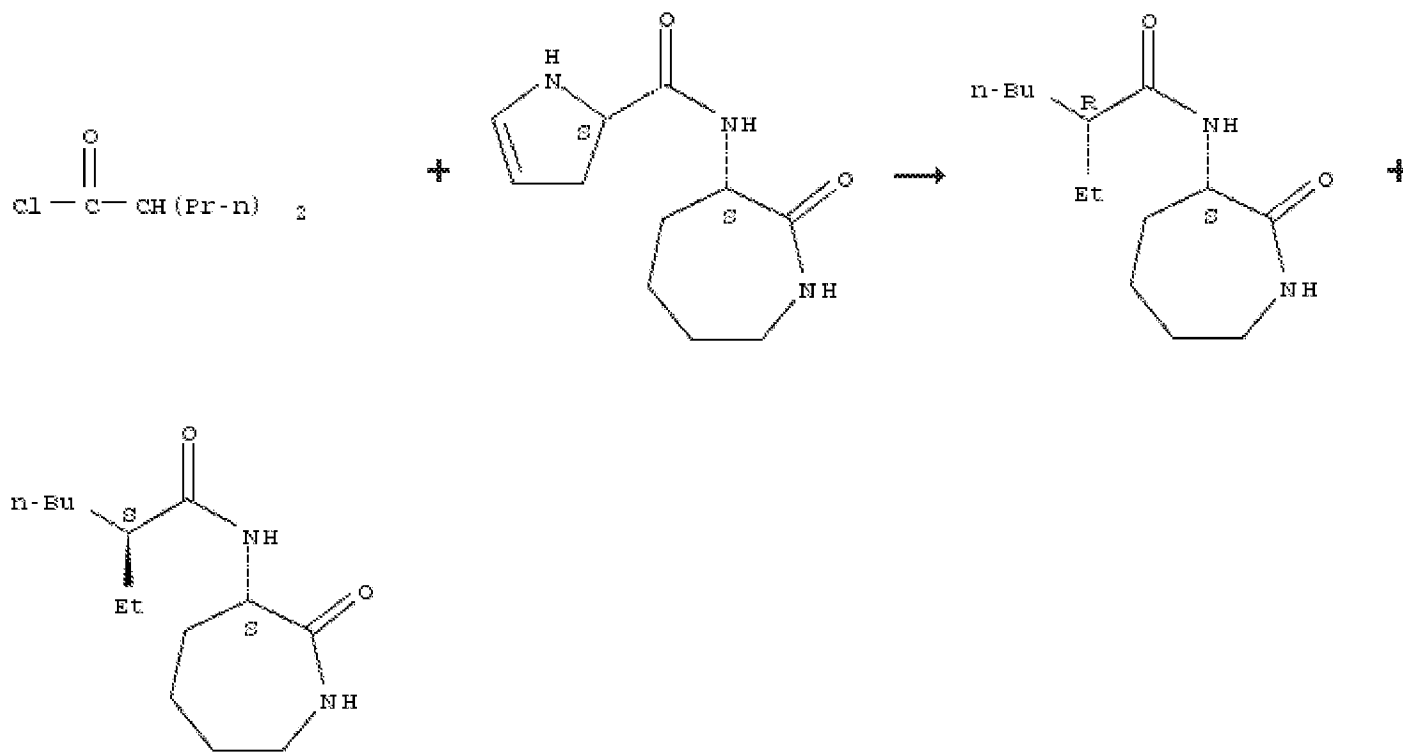
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 45: (S)-3-(3',3'-Dimethyldodecanoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate 2 (5 mmol) and Na₂CO₃ (15 mmol) in water (15 ml) were added to a solution of 3,3-dimethyldodecanoyl chloride (5 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂SO₄ and reduced in vacua. The residue was recrystallised from hexane to give (S)-3-(3',3'-dimethyldodecanoyl)amino-caprolactam (1.14 g, 68%) (S)-3-(3',3'-Dimethyldodecanoyl)amino-caprolactam, Yield (1.14 g, 68%). m.p. (hexanes) 123-125 °C; [α]_D²⁵ (c = 1, CHCl₃) +28.6; ν_{max}/cm⁻¹ 3279 (NH), 1646 (CO), 1498 (NH); δ_H (500 MHz, CDCl₃) 6.81 (1H, d, J 5.5, CHNR), 6.59-6.42 (1H, br m, CH₂NH), 4.50 (1H, ddd, J₁₁, 6, 1.5, CHNH), 3.30-3.16 (2H, m, CH₂NH), 2.08-2.02 (3H, m, CH₂CO + lactam ring CH), 2.00-1.90 (1H, m, lactam ring CH), 1.86-1.75 (2H, m, lactam ring CH x2), 1.47-1.31 (2H, br m, lactam ring CH x2), 1.30-1.17 (16H, m, (CH₂)₈), 0.89 (6H, s, C(CH₃)₂) and 0.84 (3H, t, J 7, CH₂SO₂); δ_c (125 MHz, CDCl₃) 175.8, 170.9 (CO), 52.0 (NHCH), 48.4, 42.6, 41.1 (CH₂), 33.3 (CMe₂), 31.9, 31.7, 30.4, 29.7, 29.6, 29.3, 28.9, 27.9 (CH₂), 27.3 (x2) (CH₃), 24.1, 22.6 (CH₂) and 14.1 (CH₃); m/z (M⁺ C₂₀H₃₈N₂O₂ requires 338.2933) 338.2928.

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42. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 12 h, rt

Notes

1) combined yield = 26%, reaction from p.39 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

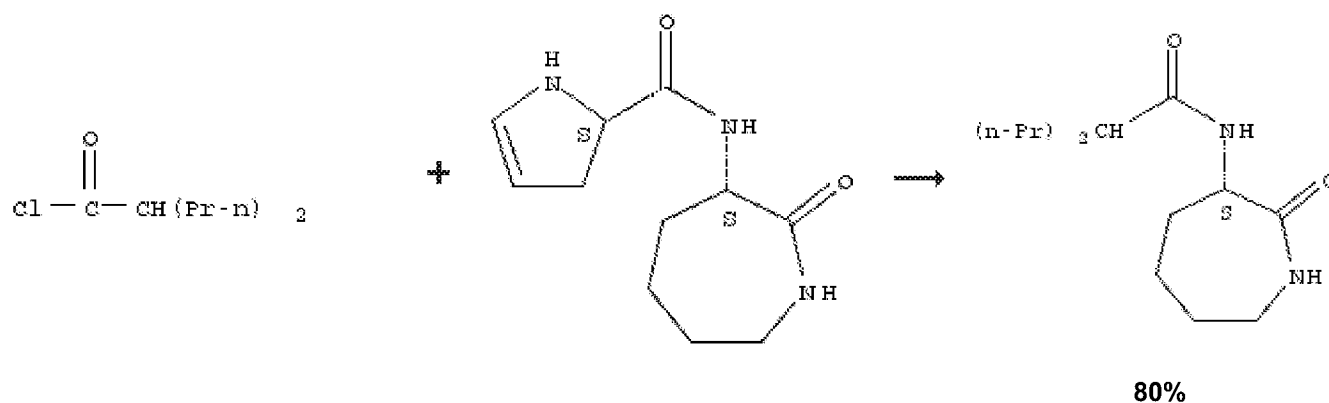
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 42(a): (3S,2'R) and Example 42(b): (3S',2'R)-3-(2'-Ethylhexanoyl)amino-caprolactam: (S,S)-S-amino-caprolactam hydro-pyrrolidine-5-carboxylate (5 mmol) and Na₂CO₃ (15 mmol) in water (15 ml) were added to a solution of (+/-) 2-ethylhexanoyl chloride (5 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂SO₄ and reduced in vacuo. The residue was recrystallised from hexane to give a mixture of (ZS,2'R) and (3S,2'S)-3-(2'-ethylhexanoyl)amino-caprolactam (328 mg, 26%). Example 42(a): (3S,2'R) and Example 42(b): (3S',2'R)-3-(2'-Ethylhexanoyl)amino-caprolactam, Yield (328 mg, 26%). $\nu_{\text{max}}/\text{cm}^{-1}$ 3306 (NH), 1686, 1633 (CO), 1537 (NH); δ_{H} (500 MHz, CDCl₃) 6.89 (2H, d, J 5, CHNH, both isomers), 6.53 (2H, br s, CH₂NH, both isomers), 4.52 (2H, ddd, J11, 6, 1.5, CHNH, both isomers), 3.30-3.16 (4H, m, CH₂NH, both isomers), 2.06 (2H, br d, J13.5, lactam CH \times 2, both isomers), 2.02-1.92 (4H, m, (CH₂)₂CHCO \times 2 and lactam ring CH \times 2, both isomers), 1.86-1.74 (4H, m, lactam ring CH \times 4, both isomers), 1.63-1.50 (4H, m, sidechain CH₂), 1.50-1.30 (8H, m, lactam ring CH \times 4+ sidechain CH₂ \times 4, both isomers), 1.30-1.14 (8H, m, side chain CH₂ \times 8, both isomers), 0.85 (3H, t, J 7.5, CH₃, one isomer) and 0.82 (3H, t, J7.5, CH₃, one isomer); δ_{C} (125 MHz, CDCl₃) 175.8, 175.1 (CO), 52.0, 51.9 (NHCHCO), 49.3 (\times 2) (CH), 42.0 (\times 2), 32.5, 32.3, 31.7 (\times 2), 29.7 (\times 2), 28.8 (\times 2), 27.9 (\times 2), 26.1, 25.9, 22.7 (\times 2), 14.0, 13.9 (CH₃) and 12.0 (\times 2)(CH₃); m/z (M+ C₁₄H₂₆N₂O₂ requires 254.1994) 254.1995.

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43. Single Step



Overview

Steps/Stages

Notes

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 12 h, rt

1) reaction from p.39 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

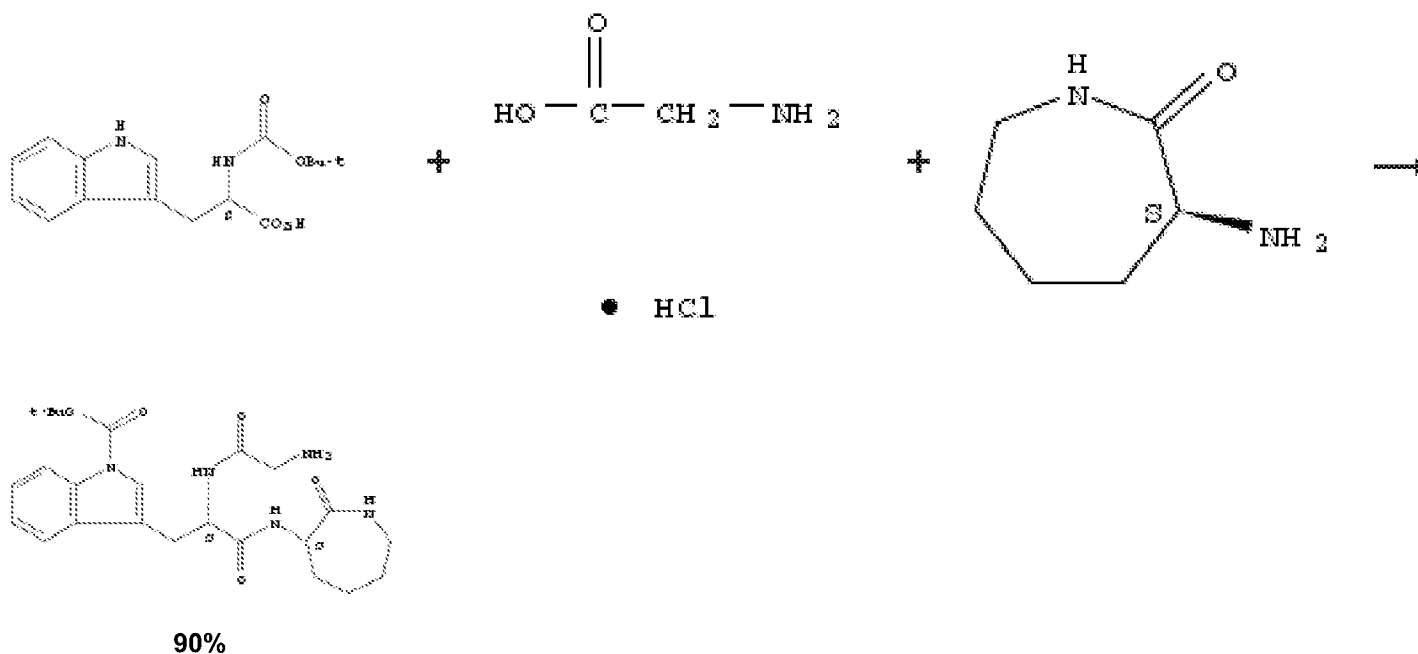
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 41: (S)-3-(2'-Propylpentanoyl)amino-caprolactam: (S,S)-3-amino-caprolactamhydro-pyrrolidine-3-carboxylate (5 mmol) and Na₂CO₃ (15 mmol) in water (15 ml) were added to a solution of 2-propylpentanoyl chloride (5 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂SO₄ and reduced in vacuo. The residue was recrystallised from hexane to give (S)-3-(2'-propylpentanoyl)amino-caprolactam (1.02 g, 80%). (S)-3-(2'-Propylpentanoyl)amino-caprolactam, Yield (1.02 g, 80%). m.p. (hexanes) 114-118 °C; [α]_D²⁵ (c = 1, CHCl₃) +29.4; ν_{max} /cm⁻¹ 3303 (NH), 1686, 1633 (CO), 1537 (NH); δ H (500 MHz, CDCl₃) 6.88 (1H, d, J 5.5, CHNH), 6.52 (1H, br s, CH₂NH), 4.52 (1H, ddd, J₁₁, 6, 1.5, CHNH), 3.30-3.16 (2H, m, CH₂NH), 2.13-2.02 (2H, m, (CH₂)₂CHCO and lactam ring CH), 2.02-1.92 (1H, m, lactam ring CH), 1.86-1.74 (2H, m, lactam ring CH x2), 1.57-1.50 (2H, m, sidechain CH₂), 1.42 (1H, br qd, J_{13.5}, 3.5, lactam ring CH), 1.38-1.29 (2H, m, lactam ring CH + side chain CH₂), 1.29-1.19 (4H, m, sidechain CH x4), 0.85 (3H, t, J_{7.5}, CH₃) and 0.84 (3H, t, J_{7.5}, CH₃); δ c (125 MHz, CDCl₃) 175.8, 175.2 (CO), 51.9 (NHCHCO), 47.2 (CH), 42.1, 35.3, 35.1, 31.7, 28.9, 27.9, 20.7 (x2) (CH₂), and 14.1 (x2)(CH₃); m/z (MH⁺ C₁₄H₂₇N₂O₂ requires 255.2073) 255.2083.

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44. Single Step



Overview

Steps/Stages

Notes

1) solid-supported reaction, solid-phase automated peptide synthesizer used, reaction from p.35 in patent, Reactants: 3, Steps: 1, Stages: 3, Most stages in any one step: 3

References

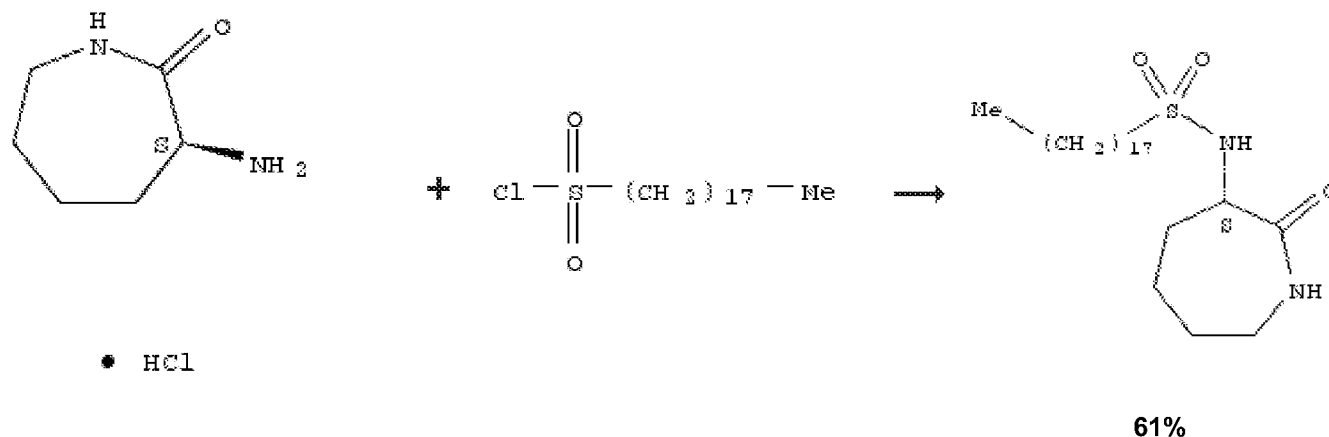
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 33: (S)-aminocaprolactam-Glycine-(L)-N(Boc)-Tryptophan: This tripeptide was made on a solid-phase automated peptide synthesizer using (S)-aminocaprolactam for the final peptide coupling step. Mr(Calc) = 471.5110. Observed Mr by mass spectrometry 471.6. Purity (%TIC in molecular ion peak) = 90% (S)-aminocaprolactam-Glycine-(L)-N(Boc)-Tryptophan, Yield 471.6. 90%.

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45. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 10 h, rt

Notes

1) reaction from p.35 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

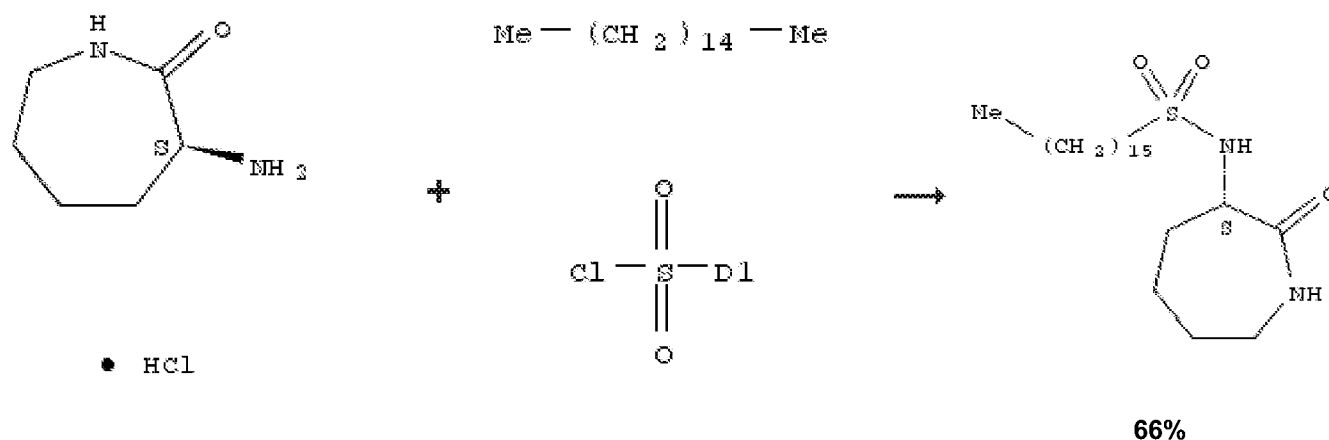
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 32: (S)-3-(Octadecanesulfonyl)amino-caprolactam: (S)-3-amino-caprolactam hydrochloride (2 mmol) and Na₂CO₃ (6 mmol) in water (20 ml) were added to a solution of octadecanesulfonylchloride (2 mmol) in dichloromethane (20 ml) at ambient temperature and the reaction was stirred for 10 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacuo. The residue was purified by silica column chromatography (hexanes:EtOAc 3:1 to 100% EtOAc) and then by recrystallisation from heptane to give (S)-3-(octadecanesulfonyl)amino-caprolactam (545 mg, 61%). (S)-3-(Octadecanesulfonyl)amino-caprolactam, Yield (545 mg, 61%). m.p. 99-100 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ 3356, 3249 (NH), 1659 (CO), 1323, 1140 (SO₂N); δ_{H} (500 MHz, CDCl₃) 6.15 (1H, t, J 6, CH₂NH), 5.69 (1H, d, J 6, CHNH), 4.12 (1H, ddd, J 11.5, 6, 2, CHNH), 3.30-3.18 (2H, m, CH₂NH), 2.97-2.92 (2H, m, CH₂SO₂), 2.12-2.07 (1H, m, ring CH), 2.06-1.97 (1H, m, ring CH), 1.87-1.56 (5H, m, CH₂CH₂SO₂ + 3 ring CH), 1.42-1.32 (3H, m, ring CH + chain CH₂), 1.32-1.18 (28H, m, chain CH₂) and 0.86 (3H, m, CH₃); m/z (MNa⁺ C₂₄H₄₈N₂O₃Na requires 467.3277852) 467.330047.

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46. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 10 h, rt

Notes

1) reaction from p.34 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

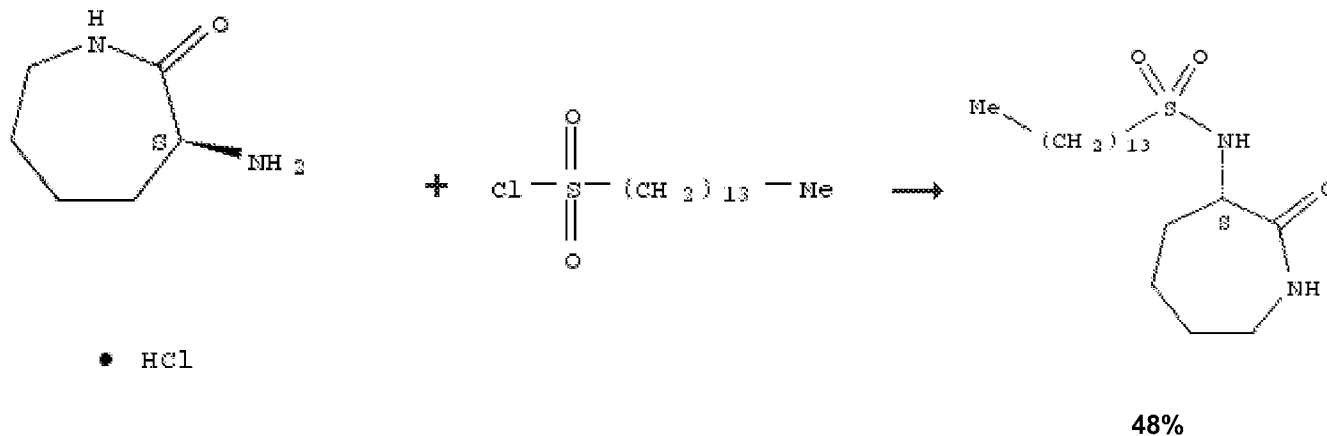
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 31; (S)-3-(Hexadecanesulfonyl)amino-caprolactam: (6)-3-amino-caprolactam hydrochloride (2 mmol) and Na₂CO₃ (6 mmol) in water (20 ml) were added to a solution of hexadecanesulfonylchloride (2 mmol) in dichloromethane (20 ml) at ambient temperature and the reaction was stirred for 10 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over 1N Na₂CO₃ and reduced in vacuo. The residue was purified by silica column chromatography (hexanes:EtOAc 3:1 to 100% EtOAc) and then by recrystallisation from heptane to give (S)-3-(hexadecanesulfonyl)amino-caprolactain (553 mg, 66%). (S)-3-(hexadecanesulfonyl)amino-caprolactain, Yield (553 mg, 66%). m.p. 100-101 °C; [α]_D²⁵ (c = 1, CHCl₃) +14.1; ν_{max}/cm⁻¹ 3356, 3249 (NH), 1659 (CO), 1323, 1140 (SO₂N); δ_H (500 MHz, CDCl₃) 6.55 (1H, t, J₆, CH₂NH), 5.76 (1H, d, J₆, CHNH), 4.1-1 (1H, ddd, J 11.5, 6, 2, CHNH), 3.30-3.17 (2H, m, CH₂NH), 2.94 (2H, t, J₈, CH₂SO₂), 2.12-2.04 (1H, m, ring CH), 2.04-1.97 (1H, m, ring CH), 1.87-1.58 (5H, m, CH₂CH₂SO₂+ 3 ring CH), 1.42-1.32 (3H, m, ring CH + chain CH₂), 1.32-1.18 (24H, m, chain CH₂) and 0.86 (3H, m, CH₃); δ_c (125 MHz, CDCl₃) 174.9 (CO) 55.5 (NHCHCO), 53.5 (CH₂SO₂), 42.1 (NCH₂), 33.8, 31.9, 29.7 (x2), 29.6 (x4), 29.5, 29.3 (x2), 29.1, 28.6, 28.3, 27.9, 23.5, 22.7 (CH₂), and 14.1 (CH₃); m/z (MNa+ C₂₀H₄₀N₂O₃Na requires 439.2965) 439.2980; anal (C₂₂H₄₄N₂O₃S requires C, 63.4, H, 10.6, N, 6.7) C, 63.1, H, 10.6, N, 6.6.

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47. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 10 h, rt

Notes

1) reaction from p.34 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

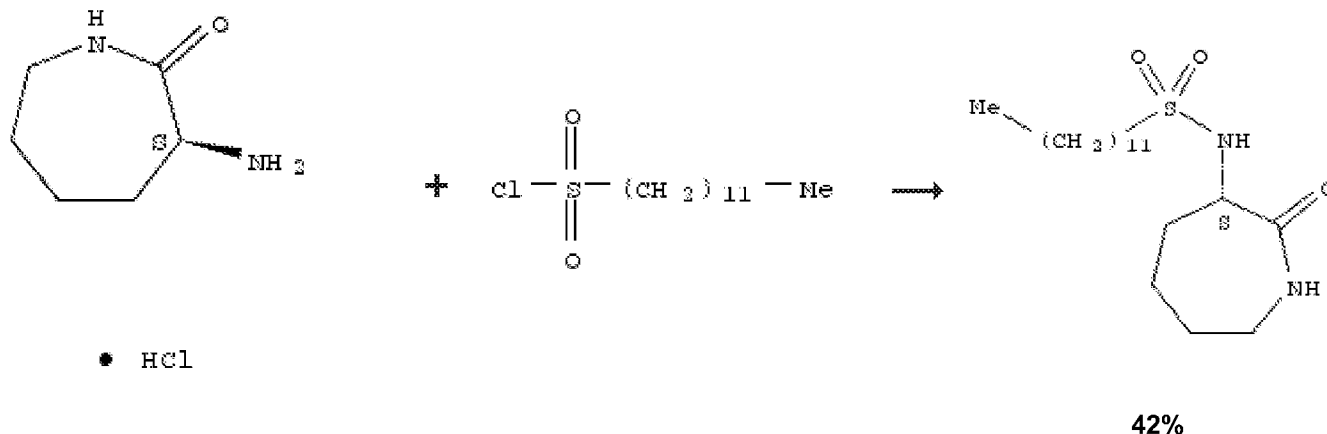
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 30: (S)-3-(Tetradecanesulfonyl)amino-caprolactam: (S)-3-amino-caprolactam hydrochloride (2 mmol) and Na₂CO₃ (6 mmol) in water (20 ml) were added to a solution of tetradecanesulfonylchloride (2 mmol) in dichloromethane (20 ml) at ambient temperature and the reaction was stirred for 10 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacuo. The residue was purified by silica column chromatography (hexanes:EtOAc 3:1 to 100% EtOAc) and then by recrystallisation from heptane to give (S)-3-(tetradecanesulfonyl)amino-caprolactam (373 mg, 48%). (S)-3-(Tetradecanesulfonyl)amino-caprolactam, Yield (373 mg, 48%). m.p. 100-101 °C; [α]_D²⁵ (c = 1, CHCl₃) +14.4; ν_{max}/cm⁻¹ 3361, 3250 (NH), 1658 (CO), 1324, 1140 (SO₂N); δ_H (500 MHz, CDCl₃) 6.64 (1H, t, J₆, CH₂NH), 5.74 (1H, d, J₆, CHNH), 4.11 (1H, ddd, J_{11.5}, 6, 2, CHNH), 3.30-3.17 (2H, m, CH₂NH), 2.97-2.92 (2H, m, CH₂SO₂), 2.12-2.05 (1H, m, ring CH), 2.05-1.96 (1H, m, ring CH), 1.87-1.59 (5H, m, CH₂CH₂SO₂ + 3 ring CH), 1.42-1.32 (3H, m, ring CH + chain CH₂), 1.32-1.18 (20H, m, chain CH₂) and 0.86 (3H, m, CH₃); δ_c (125 MHz, CDCl₃) 174.9 (CO) 55.5 (NHCHCO), 53.4 (CH₂SO₂), 42.2 (NCH₂), 33.8, 31.9, 29.6 (x4), 29.5, 29.3 (x2), 29.1, 28.6, 28.3, 27.9, 23.5, 22.7 (CH₂), and 14.1 (CH₃); m/z (MNa⁺ C₂₀H₄₀N₂O₃Na requires 411.2652) 411.2655; anal (C₂₀H₄₀N₂O₃S requires C, 61.8, H, 10.4, N, 7.2) C, 61.9, H, 10.5, N, 7.2.

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48. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 10 h, rt

Notes

1) reaction from p.33 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

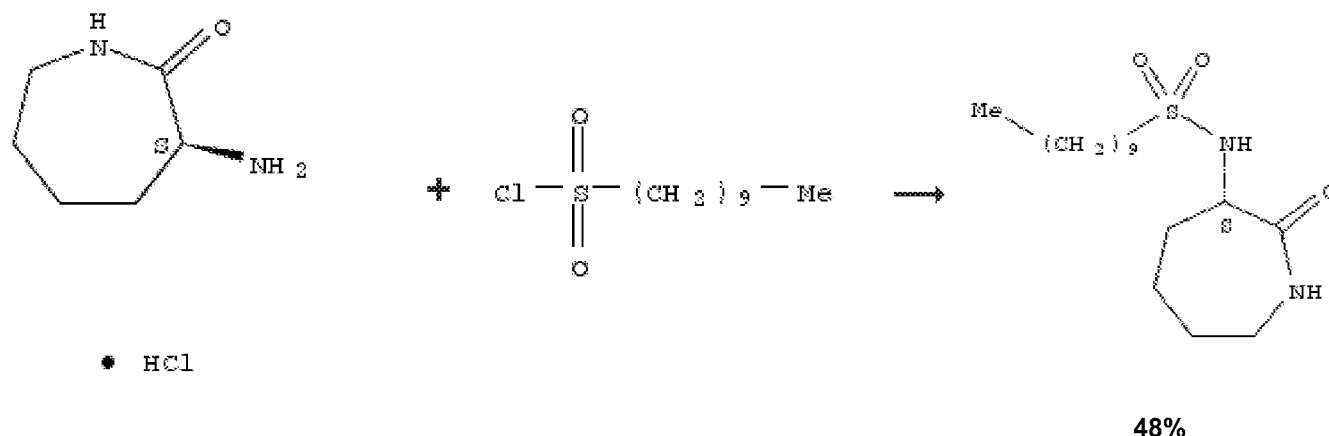
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 29: (S)-3-(Dodecanesulfonyl)amino-caprolactam: (S)-3-amino-caprolactam hydrochloride (2 mmol) and Na₂CO₃ (6 mmol) in water (20 ml) were added to a solution of dodecanesulfonylchloride (2 mmol) in dichloromethane (20 ml) at ambient temperature and the reaction was stirred for 10 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacuo. The residue was purified by silica column chromatography (hexanes:EtOAc 3:1 to 100% EtOAc) and then by recrystallisation from heptane to give (S)-3-(dodecanesulfonyl)amino-caprolactam (302 mg, 42%). (S)-3-(Dodecanesulfonyl)amino-caprolactam, Yield (302 mg, 42%). m.p. 100-101 °C; [α]_D²⁵ (c = 1, MeOH) +22.4; ν_{max}/cm⁻¹ 3366, 3247 (NH), 1657 (CO), 1324, 1143 (SO₂N); δ_H (500 MHz, CDCl₃) 6.66 (1H, t, J₆, CH₂NH), 5.78 (1H, d, J₆, CHNH), 4.10 (1H, ddd, J₁₁, 6, 2, CHNH), 3.29-3.17 (2H, m, CH₂NH), 2.97-2.90 (2H, m, CH₂SO₂), 2.12-2.03 (1H, m, ring CH), 2.03-1.96 (1H, m, ring CH), 1.88-1.59 (5H, m, CH₂CH₂SO₂ + 3 ring CH), 1.43-1.32 (3H, m, ring CH + chain CH₂), 1.32-1.18 (16H, m) and 0.85 (3H, m, CH₃); δ_C (125 MHz, CDCl₃) 175.0 (CO) 55.5 (NHCHCO), 53.5 (CH₂SO₂), 42.1 (NCH₂), 33.8, 31.8, 29.6 (x2), 29.5, 29.3 (x2), 29.1, 28.6, 28.3, 27.9, 23.5, 22.6 (CH₂), and 14.1 (CH₃); m/z (MNa⁺ C₁₈H₃₆N₂O₃Na requires 383.2339) 383.2351; ana1 (C₁₈H₃₆N₂O₃S requires C, 60.0, H, 10.1, N, 7.8) C, 59.9, H, 10.2, N, 7.7.

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49. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 10 h, rt

Notes

1) reaction from p.33 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

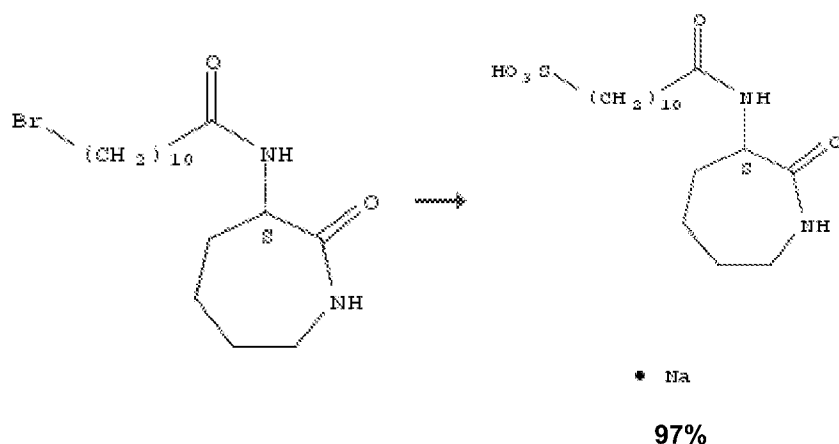
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 15 Jun 2005

Experimental Procedure

Example 28: (S)-3-(Decanesulfonyl)amino-caprolactam: (5)-3-amino-caprolactam hydrochloride (3 mmol) and Na₂CO₃ (9 mmol) in water (20 ml) were added to a solution of decanesulfonylchloride (3 mmol) in dichloromethane (20 ml) at ambient temperature and the reaction was stirred for 10 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacuo. The residue was purified by recrystallisation from EtOAc / hexanes to give (S)-3-(decanesulfonyl)amino-caprolactam (481 mg, 48%). (S)-3-(Decanesulfonyl)amino-caprolactam, Yield (481 mg, 48%). m.p. 98-99 °C; [α]_D²⁵ (c = 1, MeOH) +22.7; ν_{max} /cm⁻¹ 3365, 3248 (NH), 1657 (CO), 1324, 1142 (SO₂N); δ H (500 MHz, CDCl₃) 6.35-6.18 (1H, m, CH₂NH), 5.71 (1H, d, J 6, CHNH), 4.11 (1H, ddd, J 11.5, 6, 2, CHNH), 3.31-3.18 (2H, m, CH₂NH), 2.98-2.92 (2H, m, CH₂SO₂), 2.09 (1H, br d, J 14, ring CH), 2.06-1.97 (1H, m, ring CH), 1.88-1.59 (5H, m, CH₂CH₂SO₂ + 3 ring CH), 1.43-1.33 (3H, m, chain CH₂ + ring CH), 1.32-1.18 (12H, m, CH₃(CH₂)₆) and 0.86 (3H, m, CH₃); δ C (125 MHz, CDCl₃) 174.8 (CO) 55.5 (NHCHCO), 53.5 (CH₂SO₂), 40.7 (NCH₂), 33.9, 31.8, 29.4, 29.3, 29.2, 29.1, 28.6, 28.3, 27.9, 23.5, 22.6 (CH₂), and 14.1 (CH₃); m/z (MNa+ C₁₅H₃₂N₂O₃SNa requires 355.2031) 355.2054; anal (C₁₆H₃₂N₂O₃S requires C, 57.8, H, 9.7, N, 8.4) C, 57.8, H, 9.7, N, 8.3.

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50. Single Step



Overview

Steps/Stages

1.1 R:Na₂SO₃, S:H₂O, S:EtOH, 14 h, reflux; cooled

Notes

1) reaction from p.32 in patent, Reactants: 1, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

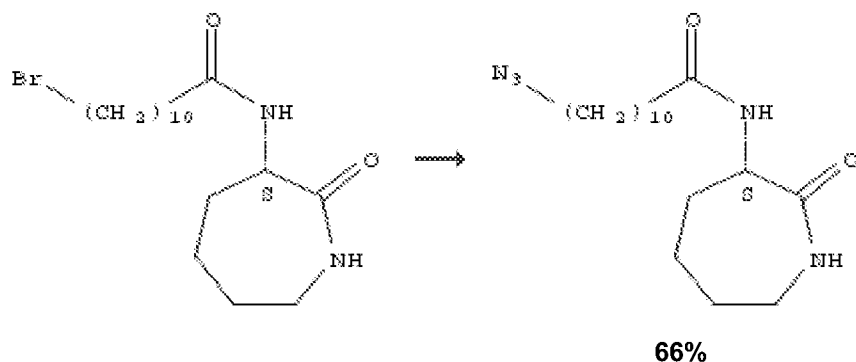
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 15 Jun 2005

Experimental Procedure

Example 27: (5) Sodium 3-(undecanoyl)amino-caprolactam 11'-sulfonate tetrahydrate: sodium sulfite (630 mg, 5 mmol) in water (3 ml) was added to (1S)-3-(11-bromoundecanoyl) amino-caprolactam (375 mg, 1 mmol) in ethanol (2 ml) and the mixture was heated at reflux for 14 hours. The cooled reaction mixture was then added to ethanol (25 ml) and the reaction was filtered. The solvent was then removed in vacuo to give (S) Sodium 3-(undecanoyl)amino-caprolactam 11'-sulfonate tetrahydrate (456 mg, 97%) (S) Sodium 3-(undecanoyl)amino-caprolactam 11'-sulfonate tetrahydrate, Yield (456 mg, 97%). m.p. (EtOAc) 208-210 °C; $[\alpha]_D^{25}$ (c = 1, H₂O) -15.5; ν_{max} /cm⁻¹ 3430, 3344, 3289 (NH + H₂O), 1667, 1643 (CO), 1530 (NH) 1195, 1183 (SO₃, asym.), 1064 (SO₃, sym.); δ H (500 MHz, d₆-DMSO) 7.76 (1H, t, J 6, CH₂NH), 7.70 (1H, d, J 7, CHNH), 4.35 (1H, dd, J 10, 7.5, CHNH), 3.42 (8H, s, 4 × H₂O) 3.17-3.00 (2H, m, CH₂NH), 2.47-2.38 (2H, m, CH₂SO₃), 2.17-2.05 (2H, m, CH₂CONH), 1.82 (1H, br s, J 13.5, C-5 H), 1.75-1.66 (2H, m, C-4 H, C-6 H), 1.65- 1.50 (3H, m, C-5 H + chain CH₂), 1.47-1.40 (2H, m, chain CH₂) 1.35 (1H, qd, J 13, 3, C-4 H), and 1.30-1.11 (13H, m, (CH₂), + C-6 H); Sc (125 MHz, d₆-DMSO) 174.5 (CO-ring), 171.5 (CO-chain), 51.6 (CH₂SO₃), 51.4 (NHCHCO), 40.8 (NCH₂), 35.3, 31.3, 29.1 (×3), 29.0 (×2), 28.8, 28.6, 27.8, 25.5 and 25.1 (CH₂); m/z MNa⁺ C₁₇H₃₁N₂O₅SSNa₂ requires 421.1749) 421.1748.

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51. Single Step



Overview

Steps/Stages

1.1 R:NaN₃, S:DMF, 14 h, 60°C

Notes

1) reaction from p.31 in patent, Reactants: 1, Reagents: 1, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

References

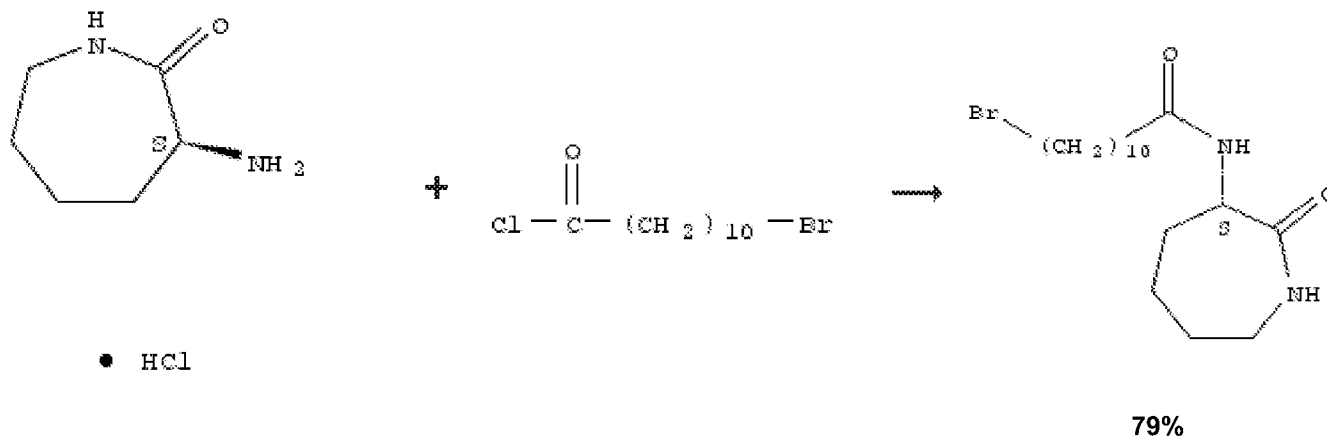
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 26: (S)-3-(11'-azido-undecanoyl)amino-caprolactam: Sodium azide (650 mg, 10 mmol) was added to (S)-3-(11-bromoundecanoyl) amino-caprolactam (375 mg, 1 mmol) in DMF (2 ml) and the mixture was heated at 60 °C for 14 hours. The solvent was then removed in vacuo and the residue was partitioned between water (20 ml) and EtOAc (3 x 20 ml). The combined organic layers were washed with 1M HCl aq (2 x 20 ml) and then dried over Na₂CO₃ and reduced in vacuo. The residue was purified by recrystallisation from EtOAc to give (S)-3-(11'-azido-undecanoyl)amino-caprolactam (221 mg, 66%). (S)-3-(11'-azido-undecanoyl)amino-caprolactam, Yield (221 mg, 66%). m.p. (EtOAc) 71-72 °C; [α]_D²⁵ (c= 1, CHCl₃) +34.7; ν_{max} /cm⁻¹ 3344, 3289 (NH), 2101 (N₃) 1668, 1631 (CO), 1516 (NH); δ H (500 MHz, d₆-DMSO) 7.77 (1H, t, J 6, CH₂NH), 7.67 (1H, d, J7, CHNH), 4.38 (1H, dd, J 11, 7, CHNH), 3.30 (2H, t, J 7, CH₂N₃), 3.15 (1H, ddd, J15.5, 10.5, 5, CHHNH), 3.05 (1H, dt, J14, 5.5, CHHNH), 2.17-2.07 (2H, m, CH₂CONH), 1.85 (1H, dt, J14, 3.5, C-5 H), 1.82-1.68 (2H, m, C-4 H, C-6 H), 1.62 (1H, qt, J 13, 3.5, C-5 H), 1.51 (4H, m, CH₂CH₂CONH and CH₂CH₂N₃), 1.36 (1H, qd, J13, 3, C-4 H), and 1.33-1.13 (13H, m, (CH₂)₆ + C-6 H); δ c (125 MHz, d₆-DMSO) 174.4 (CO-ring), 171.3 (CO-chain), 51.3 (NHCHCO), 50.7 (CH₂N₃), 40.7 (NCH₂), 35.3, 31.3, 29.0 (x2), 28.9, 28.7, 28.6, 28.3, 27.8, 26.2 and 25.4 (CH₂); m/z (MNa⁺ C₁₇H₃₁N₂O₂Na requires 360.2375) 360.2360.

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52. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 4 h, rt

Notes

1) reaction from p.31 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

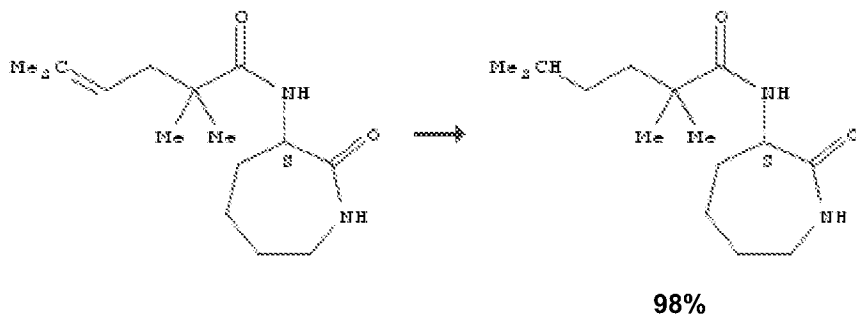
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 15 Jun 2005

Experimental Procedure

Example 25: (S)-3-(11'-bromo-undecanoyl)amino-caprolactam: (5)-3-amino-caprolactam hydrochloride (5 mmol) and Na₂CO₃ (15 mmol) in water (25 ml) were added to a solution of 11-bromo-undecanoyl chloride (5 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction was stirred for 4 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacua. The residue was purified by recrystallisation from EtOAc to give (S)-3-(11'-bromo-undecanoyl)amino-caprolactam (1.49 g, 79%). (S)-3-(11'-bromo-undecanoyl)amino-caprolactam, Yield (1.49 g, 79%). m.p. (EtOAc) 73-74 °C; [α]_D²⁵ (c = 1, CHCl₃) +31.8; ν_{max} /cm⁻¹ 3342, 3287 (NH), 1668, 1634 (CO), 1515 (NH); δ H (500 MHz, d₆-DMSO) 7.76 (1H, t, J_{6.5}, CH₂NH), 7.67 (1H, d, J 7, CHNH), 4.38 (1H, dd, J₁₁, 7, CHNH), 3.51 (2H, t, J_{6.5}, CH₂Br), 3.15 (1H, ddd, J 15.5, 10.5, 5, CHHNH), 3.05 (1H, dt, J₁₄, 7, CHHNH), 2.17-2.06 (2H, m, CH₂CONH), 1.85 (1H, dt, J₁₄, 3, C-5 H), 1.82-1.68 (4H, m, C-4 H, C-6 H and CH₂CH₂Br), 1.62 (1H, qt, J₁₂, 3.5, C-5 H), 1.46 (2H, br qn J_{6.5}, CH₂CH₂CONH), 1.41-1.31 (3H, m, C-4 H and chain CH₂) and 1.31-1.13 (11H, m, (CH₂)₈ + C-6 H); δ c (125 MHz, d₆-DMSO) 174.4 (CO-ring), 171.3 (CO-chain), 51.3 (NHCHCO), 40.7 (NCH₂), 35.3, 35.2, 32.4, 31.3, 29.0, 28.9 (x3), 28.7, 28.2, 27.8, 27.6 and 25.4 (CH₂); m/z (MH⁺ BrC₁₇H₃₂N₂O₂ requires 375.1647) 375.1655.

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53. Single Step



Overview

Steps/Stages

1.1 R:H₂, C: Pd(OH)₂, S: AcOEt, 14 h, rt

Notes

1) reaction from p.30 in patent, Reactants: 1, Reagents: 1, Catalysts: 1, Solvents: 1, Steps: 1, Stages: 1, Most stages in any one step: 1

References

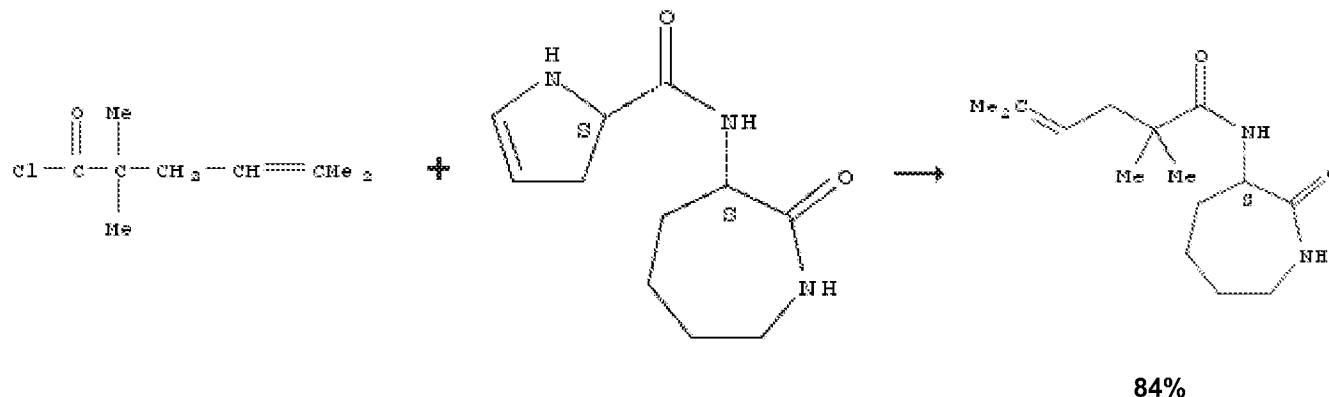
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 15 Jun 2005

Experimental Procedure

Example 24: (S)-3-(2,2',5'-Trimethyl-hexanoyl)amino-caprolactam: (S)-3-(2',2',5'-trimethyl-hex-4'-enyl)amino-caprolactam (400 mg) was dissolved in EtOAc (25 ml), palladium hydroxide-on-carbon (20%, ca 100 mg) was added, and the mixture was stirred at ambient temperature under an atmosphere of hydrogen for 14 hours. The reaction was then filtered through a Celite® pad and the solvent was removed in vacua to give (S)-3-(2,2',5'-trimethyl-hexanoyl)aminocaprolactam as a waxy solid (400 mg, 98%). (S)-3-(2,2',5'-Trimethyl-hexanoyl)amino-caprolactam, Yield (400 mg, 98%). m.p. 73-74 °C; [α]_D²⁵ (c=1, CHCl₃) +27.8; ν_{max} /cm⁻¹ 3249 (NH), 1654, 1638 (CO), 1502 (NH); δ H (500 MHz, CDCl₃) 7.08 (1H, d, J_{5.0}, CHNH), 6.75-6.55 (1H, br m, CH₂NH), 4.44 (1H, ddd, J 11, 5.5, 1.5, CHNH), 3.29-3.16 (2H, m, CH₂NH), 2.03-1.91 (2H, m, 2 × ring CH), 1.84-1.73 (2H, m, 2 × ring CH), 1.47-1.28 (5H, m, 2 × ring CH + CH₂ + CH(CH₃)₂), 1.13 (3H, s, CH₃), 1.12 (3H, s, CH₃), 1.08-1.02 (2H, m, CH₂), 0.82 (3H, s, CH₃), 0.80 (3H, s, CH₃); δ c (125 MHz, CDCl₃) 177.1, 176.1 (CO), 52.1 (NHCHCO), 42.1 (CH₂N), 41.9 (CH₂CMe₂), 39.0, 33.7, 31.5, 28.9 (CH₂), 28.4 (Me₂CH), 27.9 (CH₂), 25.3, 25.2, 22.6, 22.5 (CH₃); m/z (MH⁺ C₁₅H₂₉N₂O₂ requires 269.2229) 269.2219.

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54. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 12 h, rt

Notes

1) reaction from p.30 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

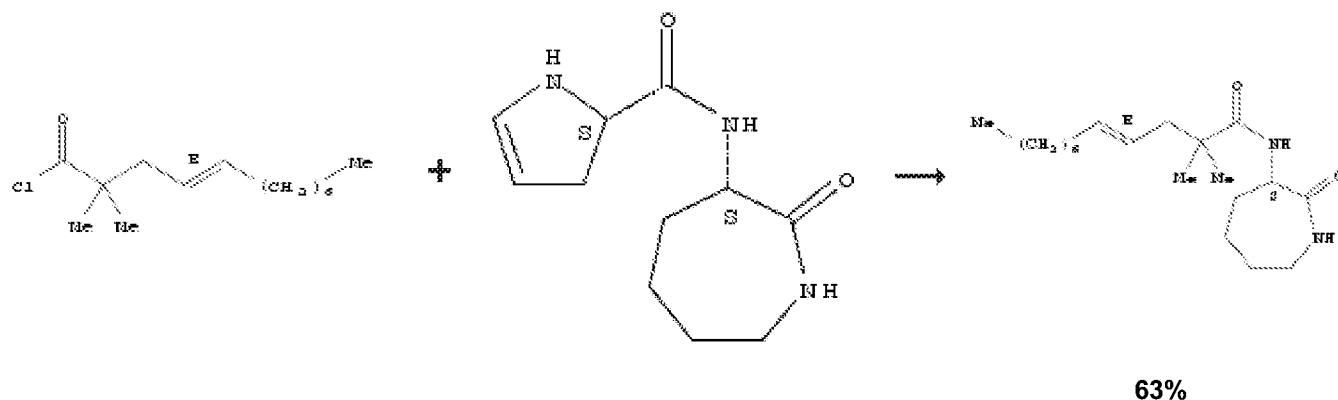
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 23: (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactamhydro-pyrrolidine-5-carboxylate (4.11 g, 16 mmol) and Na₂CO₃ (5.09 g, 48 mmol) in water (50 ml) were added to a solution of 2,2,5-trimethyl-hex-4-enoyl chloride (16 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 50 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacua. The residue was purified by silica column chromatography (1:5 EtOAc: hexanes to EtOAc) to give (S)-3-(2',2',5'-trimethyl-hex-4'-enoyl)amino-caprolactam as a waxy solid (3.58 g, 84%). (S)-3-(2',2',5'-Trimethyl-hex-4'-enoyl)amino-caprolactam, Yield (3.58 g, 84%). m.p. 43-44 °C; [α]_D²⁵ (c = 1, CHCl₃) +23.2; ν_{max}/cm⁻¹ 3394, 3251 (NH), 1674, 1633 (CO), 1503 (NH); δ_H (500 MHz, CDCl₃) 7.11 (1H, d, J_{5,0}, CHNH), 6.65-6.45 (1H, br m, CH₂NH), 5.04 (1H, t, J 7.5, CH=C), 4.44 (1H, ddd, J₁₁, 5.5, 1.5, CHNH), 3.24-3.16 (2H, m, CH₂NH), 2.20 (1H, dd, J_{14,5}, 7.5, C=CHCH₂), 2.15 (1H, dd, J, 14.5, 7.5, C-CHCH₂), 2.03-1.90 (2H, m, 2 x ring CH), 1.84-1.72 (2H, m, 2 x ring CH), 1.65 (3H, s, CH₃), 1.56 (3H, s, CH₃), 1.45-1.28 (2H, m, 2 x ring CH), 1.13 (3H, s, CH₃) and 1.12 (3H, s, CH₃); δ_C (125 MHz, CDCl₃) 176.9, 176.0 (CO), 134.1, 119.9 (CH=CH), 52.1 (NHCHCO), 42.5 (CH₂CMe₂), 42.1 (CH₂N), 39.0, 31.5, 28.9, 28.0 (CH₂ lactam), 26.0, 25.0, 24.9, 17.9 (CH₃); m/z (MH⁺ C₁₅H₂₇N₂O₂ requires 267.2073) 267.2063.

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55. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 12 h, rt

Notes

1) reaction from p.29 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

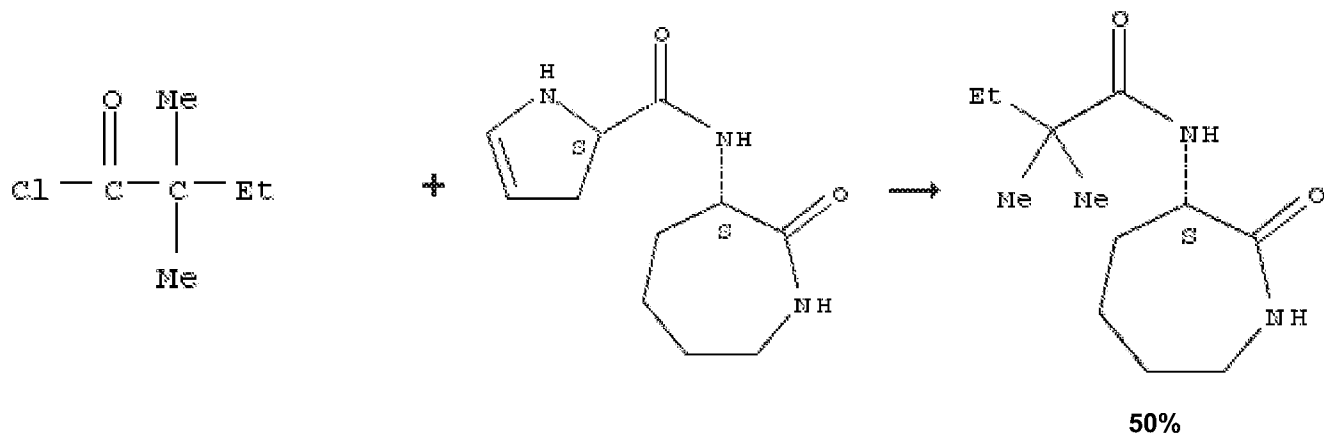
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 22: (S,E)-3-(2',2'-Dimethyl-dodec-4'-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (10 mmol) and Na₂CO₃ (3.0 mmol) in water (30 ml) were added to a solution of 2,2-dimethyl-dodec-2-enoyl chloride (crude, from above reaction) (10 mmol) in dichloromethane (30 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacuo. The residue was purified by silica column chromatography (1:1 EtOAc: hexanes to EtOAc) to give (S,E)-3-(2',2'-dimethyl-dodec-4'-enoyl)amino-caprolactam as a colourless oil (2.12 g, 63%). (S,E)-3-(2',2'-Dimethyl-dodec-4'-enoyl)amino-caprolactam, Yield (2.12 g, 63%). [α]_D²⁵ (c = 1, CHCl₃) +21.6; ν_{max}/cm⁻¹ 3264 (NH), 1639 (CO), 1497 (NH); δ_H (500 MHz, CDCl₃) 7.09 (1H, d, J 5.5, CHNH), 6.67-6.32 (1H, br m, CH₂NH), 5.42 (1H, dt, J 15, 6.5, CH=CH), 5.28 (1H, dt, J 15, 7, CH=CH), 4.44 (1H, dd, J 11, 5.5, CHNH), 3.30-3.17 (2H, m, CH₂NH), 2.20 (1H, dd, 13.5, 7, CH=CHCH₂), 2.14 (1H, dd, 13.5, 7, CH=CHCH₂), 2.01-1.87 (4H, br m, ring CH x2, + CH₂CH=CH), 1.87-1.74 (2H, m, ring CH), 1.47-1.32 (2H, m, ring CH), 1.27-1.15 (10H, br m, (CH₂)₃), 1.13 (3H, s, CMeMe), 1.12 (3H, s, CMeMe) and 0.83 (3H, t, J 7, CH₂CH₃); δ_C (125 MHz, CDCl₃) 176.8, 176.0 (CO), 134.2, 125.2 (CH=CH), 52.1 (NHCHCO), 43.9 (CH₂), 42.1 (x2)(CH₂+ CMe₂), 32.6, 31.8, 31.5, 30.1, 29.4, 29.1 (x2), 28.9, 27.9 (CH₂), 25.0, 24.8 (CH₃) and 22.6 (CH₃); m/z (MH⁺ C₂₀H₃₇N₂O₂ requires 337.2855) 337.2858.

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56. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 12 h, rt

Notes

1) reaction from p.29 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

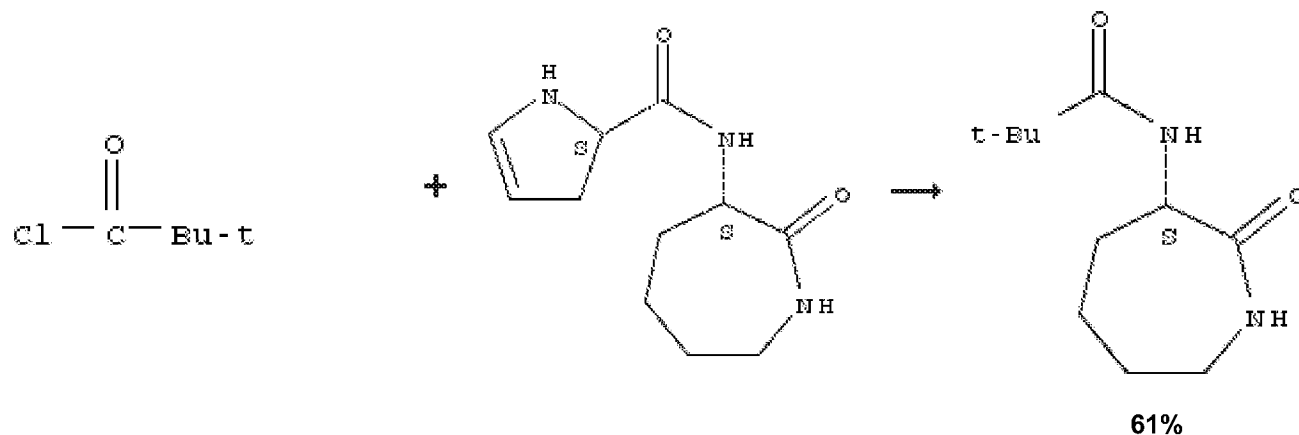
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 21: (S)-3-(2',2'-Dimethyl-buteryl)amino-caprolactam: (S,S)-3-amino-caprolactamhydro-pyrrolidine-S-carboxylate (5 mmol) and Na₂CO₃ (15 mmol) in water (15 ml) were added to a solution of 2,2-dimethyl-buteryl chloride (5 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂SO₄ and reduced in vacuo. The residue was recrystallised from EtOAc / hexane to give (S)-3-(2',2'-dimethylpropionyl) amino-caprolactam (562 mg, 50%) (S)-3-(2',2'-Dimethyl-buteryl)amino-caprolactam, Yield (562 mg, 50%). m.p. 106-107 °C; [α]_D²⁵ (c = 1, CHCl₃) +33.6; ν_{max}/cm⁻¹ 3400, 3278 (NH), 1677, 1630 (CO), 1500 (NH); δ_H (500 MHz, CDCl₃) 7.08 (1H, d, J 5.0, CHNH), 6.72 (1H, br s, CH₂NH), 4.44 (1H, ddd, J 11, 5.5, 1.5, CRNH), 3.28-3.16 (2H, m, CH₂NH), 2.04-1.90 (2H, m, 2 × ring CH), 1.83-1.72 (2H, m, 2 × ring CH), 1.57-1.44 (2H, m, CH₂CH₃), 1.44-1.30 (2H, m, 2 × ring CH), 1.12 (3H, s, CH₃) 1.11 (3H, s, CH₃) and 0.78 (3H, t, J 7.5, CH₂CH₃); δ_c (125 MHz, CDCl₃) 177.0, 176.0 (CO), 52.1 (NHCHCO), 42.2 (CCO), 42.0 (CH₂N), 33.7 (CH₂CH₃), 31.6, 28.9, 27.9 (CH₂ lactam), 24.8, 24.7 (CCH₃) and 9.1 (CH₂CH₃); m/z (MH⁺ C₁₂H₂₃N₂O₂ requires 227.1760) 227.1767.

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57. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 12 h, rt

Notes

1) reaction from p.28 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

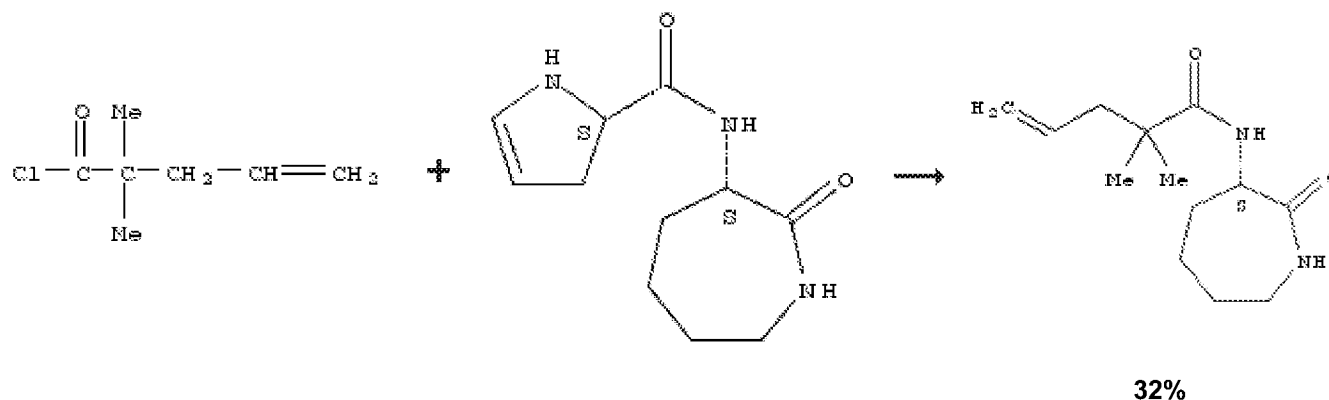
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 20: (S)-3-(2',2'-Dimethyl-propionyl)amino-caprolactam: (S,S)-3-amino-caprolactamhydro-pyrrolidine-5-carboxylate (5 mmol) and Na₂CO₃ (15 mmol) in water (15 ml) were added to a solution of 2,2-dimethyl-propionyl chloride (5 mmol) in dichloromethane (15 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂SO₄ and reduced in vacuo. The residue was recrystallised from EtOAc/hexane to give (S)-3-(2',2'-dimethyl-propionyl)aminocaprolactam (645 mg, 61%). (S)-3-(2',2'-dimethyl-propionyl)aminocaprolactam, Yield (645 mg, 61%). m.p. 126-127 °C; [α]_D²⁵ (c = 1, CHCl₃) +39.5; ν_{max}/cm⁻¹ 3381, 3255 (NH), 1680, 1632 (CO), 1506 (NH); δ_H (500 MHz, CDCl₃) 7.10 (1H, d, J 5.0, CHNH), 6.75 (1H, br s, CH₂NH), 4.42 (1H, ddd, J 11, 5.5, 1.5, CHNH), 3.27- 3.16 (2H, m, CH₂NH), 2.03-1.89 (2H, m, 2 × ring CH), 1.83-1.71 (2H, m, 2 × ring CH), 1.45-1.28 (2H, m, 2 × ring CH) and 1.15 (9H, s, 3 × CH₃); δ_C (125 MHz, CDCl₃) 177.7, 176.1 (CO), 52.1 (NHCHCO), 42.0 (CH₂N), 40.5 (CCO), 31.5, 28.9, 27.9 (CH₂ lactam), 27.4 (3 × CH₃); m/z (MNa⁺ C₁₁H₂₀N₂O₂Na requires 235.141699) 235.142237; (MH⁺ C₁₁H₂₁N₂O₂ requires 213.1597543) 213.160246.

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58. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 12 h, rt

Notes

1) reaction from p.27 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

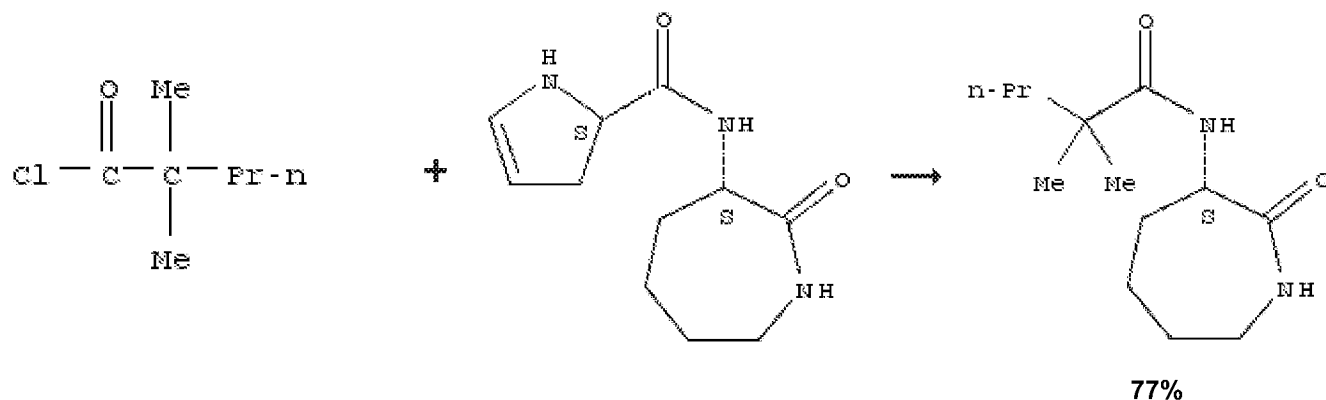
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 19 : (S)-3-(2',2'-Dimethyl-pent-4-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (20 mmol) and Na₂CO₃ (60 mmol) in water (50 ml) were added to a solution, of 2,2-dimethyl-pent-4-enoyl chloride (20 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃, and reduced in vacuo. The residue was purified by silica column chromatography (1:1 EtOAc: hexane to EtOAc) to give (S)-3-(2',2'-dimethyl-pent-4-enoyl)amino-caprolactam (1.43 g, 32%). (S)-3-(2',2'-Dimethyl-pent-4-enoyl)amino-caprolactam, Yield (1.43 g, 32%). m.p. 71-72 °C; [α]_D²⁵ (c = 1, CHCl₃) +27.7; ν_{max}/cm⁻¹ 3395, 3304 (NH), 1675, 1633 (CO), 1534 (NH); δ_H (500 MHz, CDCl₃) 7.10 (1H, d, J4.5, CHNH), 6.48 (1H, br s, CH₂NH), 5.68 (1H, ddt, J 17, 10, 7.5, CH=CH₂), 5.02 (1H, br d, J 17 CH=CHH), 5.00 (1H, br d, J10, CH=CHH), 4.45 (1H, dd, J11, 5.5, CHNH), 3.30-3.17 (2H, m, CH₂NH), 2.27 (1H, J14, 7.5, CHHCH=CH₂), 2.22 (1H, dd, J14, 7.5, CHHCH=CH₂), 2.01 (1H, br d, J13, ring CH), 1.98-1.92 (1H, m, ring CH), 1.85- 1.73 (2H, m, ring CH), 1.47-1.30 (2H, br m, ring CH x2), 1.16 (3H, s, CMeMe) and 1.15 (3H, s, CMeMe); δ_C (125 MHz, CDCl₃) 176.4, 175.9 (CO), 134.2 (CH CH₂), 117.8 (CH=CH₂), 52.1 (NHCHCO), 45.2, 42.1 (CH₂), 41.9 (CMe₂), 31.5, 28.9, 27.9 (CH₂), 25.0 and 24.9 (CH₃); m/z (M⁺ C₁₃H₂₂N₂O₂ requires 238.16813) 238.16834.

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59. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 12 h, rt

Notes

1) reaction from p.27 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

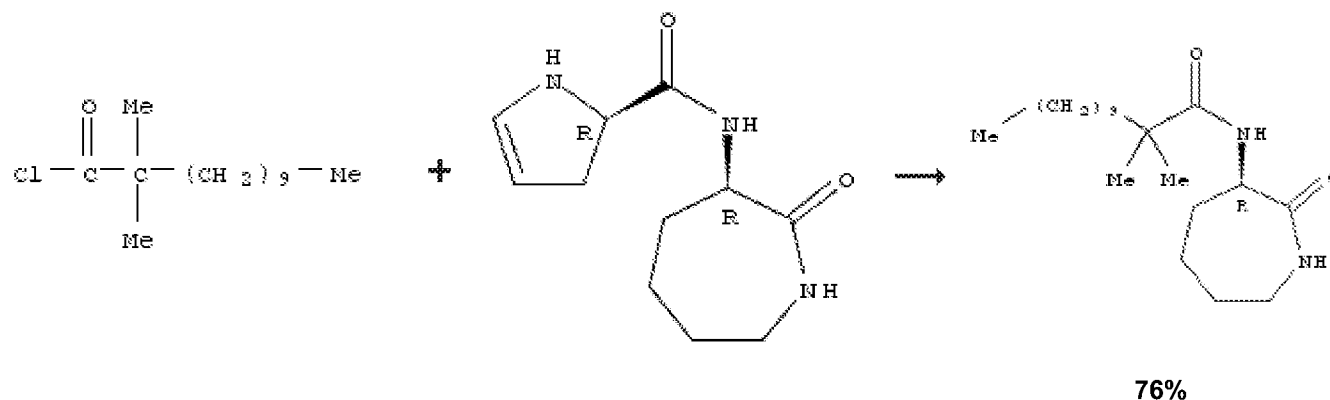
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 18 : (S)-3-(2',2'-Dimethyl-pentanoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (20 mmol) and Na₂CO₃ (60 mmol) in water (50 ml) were added to a solution of 2,2-dimethyl-pentanoyl chloride (20 mmol) in dichloromethane (50 ml) at ambient temperature and the reaction was stirred for 12 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacuo. The residue was recrystallised from EtOAc / hexane to give (S)-3-(2',2'-dimethylpentanoyl)amino-caprolactam (3.50 g, 77%) (S)-3-(2',2'-Dimethyl-pentanoyl)amino-caprolactam, Yield (3.50 g, 77%). m.p. 84-85 °C; [α]_D²⁵ (c = 1, CHCl₃) +30.7; ν_{max}/cm⁻¹ 3387, 3239 (NH), 1655, 1634 (CO), 1507 (NH); δ_H (500 MHz, CDCl₃) 7.08 (1H, d, J₅, CHNH), 6.53 (1H, br s, CH₂NH), 4.45 (1H, ddd, J₁₁, 5.5, 1.5, CHNH), 3.29-3.16 (2H, m, CH₂NH), 2.00 (1H, br d, J₁₃, ring CH), 1.98-1.92 (1H, m, ring CH), 1.84-1.73 (2H, m, ring CH), 1.47-1.30 (4H, br m, ring CH ×2 + CH₂CMe₂CONH), 1.23-1.15 (2H, m, CH₂CH₃) 1-14 (3H, s, CMeMe), 1.13 (3H, s, CMeMe) and 0.84 (3H, t, J₇, CH₂CH₃); δ_c (125 MHz, CDCl₃) 177.0, 176.1 (CO), 52.1 (NHCHCO), 43.6, 42.0 (×2, one of which is CMe₂), 31.5, 28.9, 27.9 (CH₂), 25.3, 25.2 (CH₃), 18.0 (CH₂) and 14.5 (CH₃); m/z (M⁺ C₁₃H₂₄N₂O₂ requires 240.18378) 240.18437.

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60. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 2 h, rt

Notes

1) reaction from p.27 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

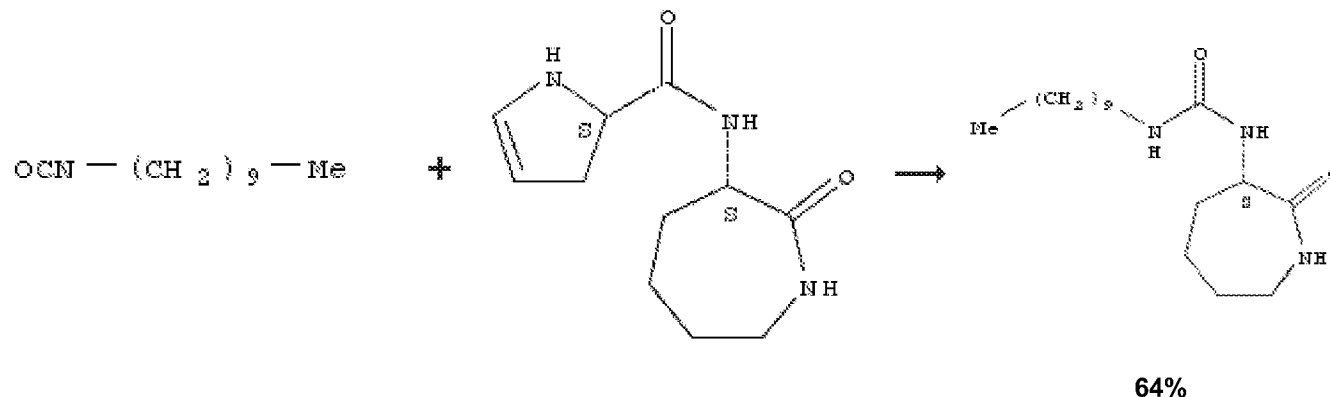
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 17: (R)-3-(2',2'-Dimethyl-dodecanoyl)amino-caprolactam: (R,R)-3-amino-caprolactamhydro-pyrrolidine-5-carboxylate (2 mmol) and Na₂CO₃ (6 mmol) in water (25 ml) were added to a solution of 2,2-dimethyl-dodecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacuo. The residue was purified by silica column chromatography (EtOAc: hexanes 1:3 to EtOAc) to give (R)-3-(2',2'-dimethyl-dodecanoyl)amino-caprolactam (515 mg, 76%). Compound 17 was later resynthesised on a larger scale, and this batch of material had the following properties: (R)-3-(2',2'-Dimethyl-dodecanoyl)amino-caprolactam, Yield (515 mg, 76%). m.p. 48-49 °C; [α]_D²⁵ (c = 1, CHCl₃) -25.7; [α]_D²⁵ (c = 0.5, MeOH) -12.2

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61. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 2 h, rt

Notes

1) reaction from p.26 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

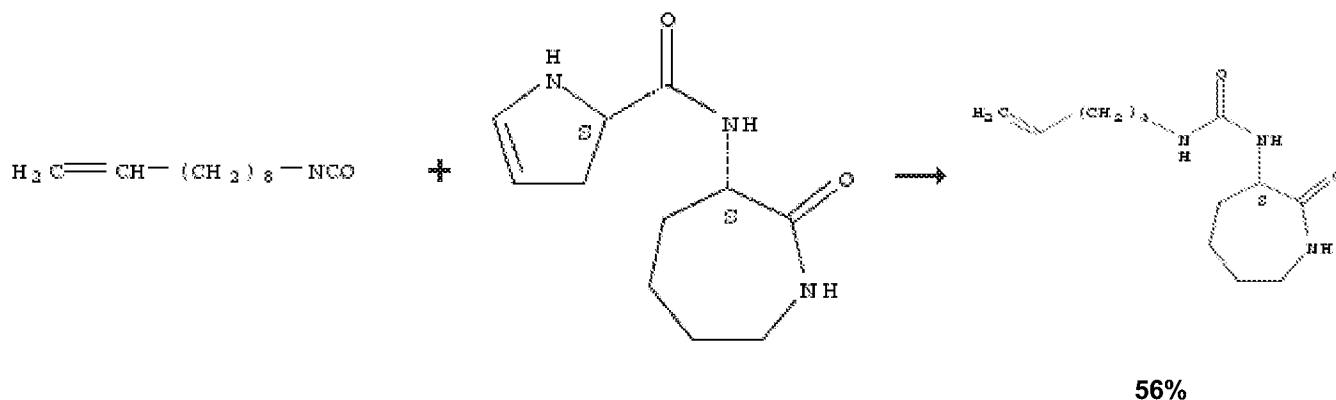
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 16: (S)-3-(decylaminocarbonyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na₂CO₃ (6 mmol) in water (25 ml) were added to a solution of decyl isocyanate (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacuo. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (401 mg, 64%). (S)-3-(decylaminocarbonyl)amino-caprolactam, Yield (401 mg, 64%). Melting point: 97-98 °C. [α]_D²⁵ (c=1, CHCl₃) = +27.7. IR: ν_{max} (cm⁻¹): 3359, 3316 (NH), 1621, (CO), 1558 (NH). ¹H NMR (δ H 500 MHz, CDCl₃): 6.62 (1H, br s, ring CH₂NH), 6.09 (1H, d, J 6 CHNH), 5.16 (1H, br t, J₅, urea CH₂NH), 4.48 (1H, ddd, J 11, 6, 1, NHCHCO), 3.26 (1H, ddd, J₁₆, 11, 5, ring CH₂N), 3.17 (1H, dt, J₁₅, 7, ring CH₂N), 3.11-3.02 (2H, m, urea NHCH₂), 2.02 (1H, br d J₁₄, ring CH), 1.96-1.87 (1H, m, ring CH), 1.83-1.70 (2H, m, ring CH), 1.48-1.27 (4H, br m, ring CH x2 + chain CH₂), 1.27- 1.14 (14H, m, (CH₂)) and 0.82 (3H, t, J 7, CH₃). ¹³C NMR (δ c, 125 MHz, CDCl₃): 177.2, 157.6 (CO), 52.7 (NHCHCO), 42.1, 40.4 (NCH₂), 32.9, 31.8, 30.2, 29.6, 29.5, 29.4, 29.3, 28.8, 27.9, 26.9, 22.6 (CH₂) and 14.1. m/z (C₁₇H₃₃N₃O₂Na): 334.24880 (calculated: 334.2470).

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62. Single Step



Overview

Steps/Stages

Notes

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 2 h, rt

1) reaction from p.25 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

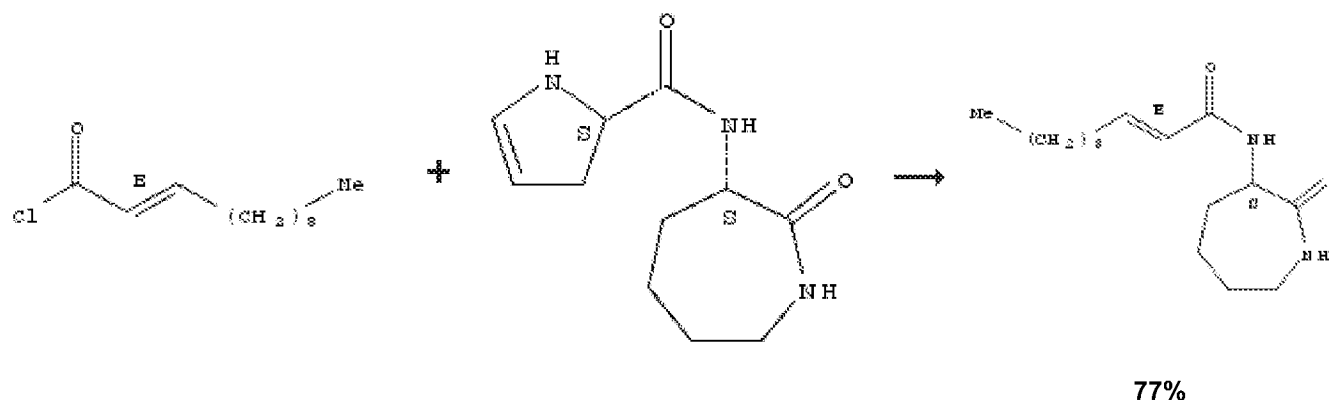
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 15: (S)-3-(dec-9-enylaminocarbonyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na₂CO₃ (6 mmol) in water (25 ml) were added to a solution of dec-9-enyl isocyanate (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacuo. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (347 mg; 56%). (S)-3-(dec-9-enylaminocarbonyl)amino-caprolactam: yield (347 mg; 56%). Melting point: 98-99 °C. [α]_D²⁵ (c=1, CHCl₃) = +27.3. IR: ν_{max} (cm⁻¹): 3365, 3327, 3276 (NH), 1619, (CO), 1551 (NH). ¹H NMR (δ H, 500 MHz, CDCl₃): 6.64 (1H, br s, ring CH₂NH), 6.12 (1H, d, J₆ CHNH), 5.75 (1H, dtd, J₁₇, 10, 6.5, 1.5, CH₂=CH), 5.21-5.12 (1H, br m, urea CH₂NH), 4.93 (1H, dq, J₁₇, 1.5, CHH=CH), 4.87 (1H, brd, J₁₀, CHH=CH), 4.49 (1H, dd, J₁₁, 6, NHCHCO), 3.25 (1H, ddd, J_{15.5}, 12, 4, ring CH₂N), 3.17 (1H, dt, J₁₄, 6, ring CH₂N), 3.11-3.02 (2H, m, urea NHCH₂), 2.05-1.87 (4H, br m, ring CH x2 + CH₂CH=CH), 1.82-1.70 (2H, m, ring CH), 1.48-1.36 (3H, br m, chain CH₂CH₂NH, + ring CH), 1.36-1.27 (3H, m, ring CH + chain CH₂) and 1.27-1.17 (8H, m, chain (CH₂)₄). ¹³C NMR (δ C, 125 MHz, CDCl₃): 177.2, 157.6 (CO), 139.1, 114.1 (CH=CH), 52.7 (NHCHCO), 42.1, 40.3 (NCH₂), 33.7, 32.9, 30.3, 29.4, 29.3, 29.0, 28.8 (x2), 27.9 and 26.9 (CH₂). m/z (C₁₇H₃₁N₃O₂Na): 332.23150 (calculated: 332.2314).

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63. Single Step



Overview

Steps/Stages

Notes

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 2 h, rt

1) reaction from p.24 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

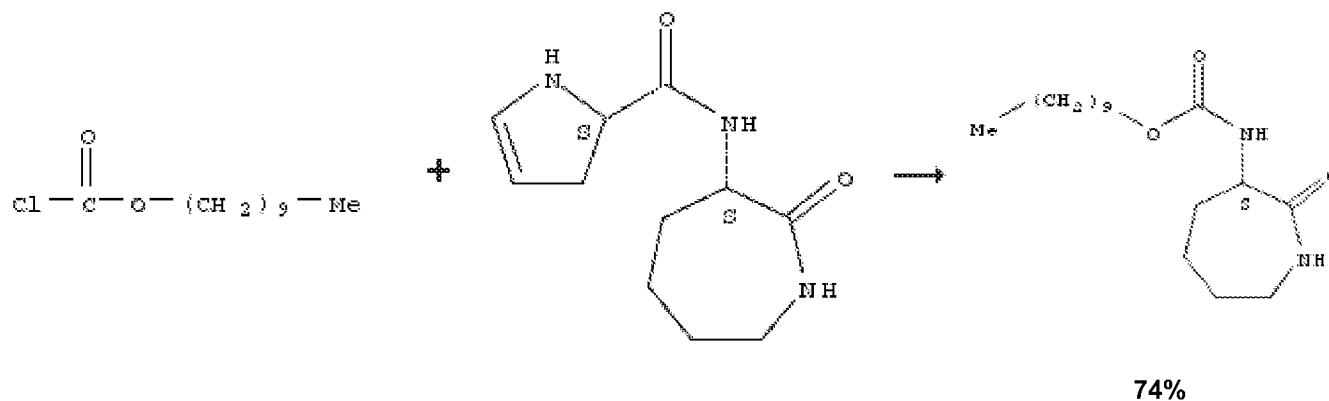
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 14: (S)-(E)-3-(dodec-2-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na₂CO₃ (6 mmol) in water (25 ml) were added to a solution of dodec-2-enoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacuo. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (472 mg; 77%). (S)-(E)-3-(dodec-2-enoyl)amino-caprolactam: Yield (472 mg; 77%). Melting point: 87-88 °C. $[\alpha]_{25D}^{c=1, CHCl_3} = +44.7$. IR: ν_{max} (cm⁻¹): 3382, 3331 (NH), 1660, 1616 (CO), 1520 (NH). ¹H NMR (δ H 500 MHz, CDCl₃): 6.94 (1H, d, J 5.5, CHNH), 6.84 (1H, br s, CH₂NR), 6.78 (1H, dt, J15.5, 7, CH₂CH=CH), 5.80 (1H, d, J 15.5, CH₂CH=CH), 4.56 (1H, ddd, J11, 6, 1.5, CHNH), 3.29-3.15 (2H, m, CH₂NH), 2.11 (2H, q, J7, CH₂CH-CH), 2.07 (1H, br d, J13.5, ring CH), 1.98-1.90 (1H, m, ring CH), 1.86-1.73 (2H, m, ring CH), 1.44 (1H, br qd, J14, 2.5, ring CH), 1.41-1.29 (3H, br m, ring CH + CH₂CH₂CH-CH), 1.29-1.14 (12H, m, (CH₂)₆) and 0.82 (3H, t, J 6.5, CH₃). ¹³C NMR (δ c, 125 MHz, CDCl₃): 175.9, 165.0 (CO), 144.8, 123.5 (CH=CH), 52.0 (NHCHCO), 42.0 (NCH₂), 32.0, 31.8, 31.6, 29.4 (x2), 29.2, 29.1, 28.8, 28.2, 27.9, 22.6 (CH₂) and 14.1 (CH₃)- m/z (C₁₈H₃₂N₂O₂Na): 331.23570 (calculated: 331.2361).

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64. Single Step



Overview

Steps/Stages

Notes

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 2 h, rt

1) reaction from p.24 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

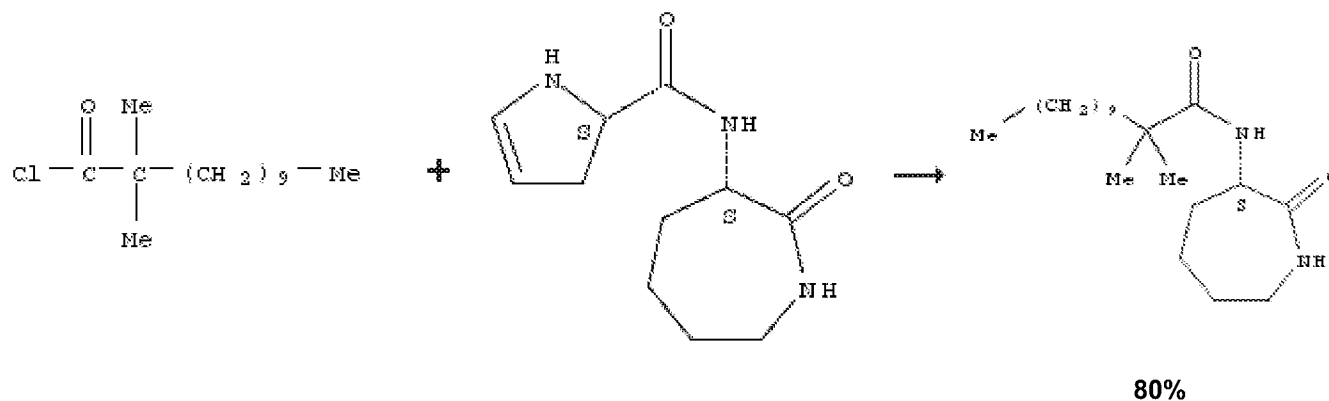
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 13: (S)-3-(decyloxycarbonyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na₂CO₃ (6 mmol) in water (25 ml) were added to a solution of decyl chloroformate (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacua. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (459 mg; 74%). (S)-3-(decyloxycarbonyl)amino-caprolactam, Yield (459 mg; 74%). Melting point: 40-41 °C. [α]_D²⁵ (c=1, CHCl₃) = +31.4. IR: ν_{max} (cm⁻¹): 3352, 3300 (NH), 1682, 1657, 1637 (CO), 1513 (NH). ¹H NMR (δ H, 500 MHz, CDCl₃): 6.86 (1H, br s, CH₂NH), 6.72 (1H, d, J 6 CHNH), 4.49 (1H, dd, J 11, 6, CHNH), 3.99 (2H, t, J 6, OCH₂), 3.26-3.14 (2H, m, CH₂NH), 2.04 (1H, br d, J 13.5, ring CH), 2.00-1.91 (1H, m, ring CH), 1.82-1.68 (2H, m, ring CH), 1.55 (2H, br gn J 7.0, CH₂CH₂O), 1.48 (1H, br qd, J 14, 2.5, ring CH), 1.38-1.31 (1H, br m, ring CH), 1.29-1.17 (14H, m, (CH₂)₄) and 0.83 (3H, t, J 7, CH₃). ¹³C NMR (δ C, 125 MHz, CDCl₃): 175.8, 155.9 (CO), 65.0 (OCH₂), 53.5 (NHCHCO), 42.0 (NCH₂), 32.1, 31.8, 29.5 (x2), 29.2 (x2), 29.0, 28.8, 28.0, 25.8, 22.6 (CH₂) and 14.1 (CH₃). m/z (C₂₇H₃₂N₂O₃Na): 335.23190 (calculated: 335.2311).

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65. Single Step



Overview

Steps/Stages

Notes

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 2 h, rt

1) reaction from p.23 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

By Grainger, David John, Fox, David John

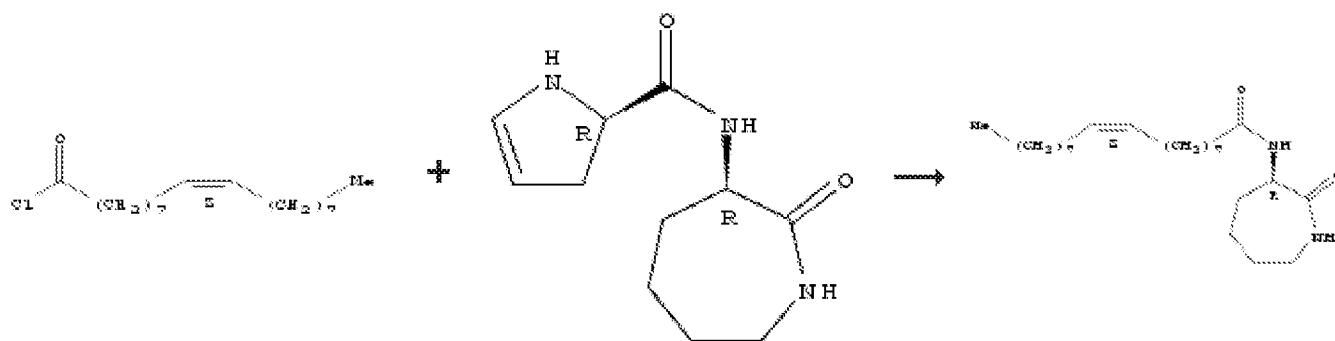
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 12: (5)-3-(2',2'-dimethyl-dodecanoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na₂CO₃ (6 mmol) in water (25 ml) were added to a solution of 2,2-dimethyl-dodecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacuo. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (543 mg; 80%). (5)-3-(2',2'-dimethyl-dodecanoyl)amino-caprolactam: Yield (543 mg; 80%). Compound 12 was later resynthesised on a larger scale, and this batch of material had the following properties Melting point: 41-42 °C. [α]_{25D} (c=1, CHCl₃) = +28.0. IR: ν_{max} (cm⁻¹): 3403, 3265 (NH), 1673, 1641 (CO), 1497 (NH). ¹H NMR (δ H 500 MHz, CDCl₃): 7.08 (1H, d, J5.5, CHNH), 6.67 (1H, br s, CH₂NH), 4.44 (1H, dd, J11, 5.5, CHNH), 3.28-3.15 (2H, m, CH₂NH), 2.01 (1H, br d, J13, ring CH), 1.98-1.89 (1H, m, ring CH), 1.84-1.72 (2H, m, ring CH), 1.47- 1.30 (3H, br m, ring CH + CH₂CMe₂CONH), 1.27-1.15 (17H, br m, ring CH + (CH₂)₈) 1.13 (3H, s, CMeMe), 1.12 (3H, s, CMeMe) and 0.82 (3H, t, J7, CH₂CH₃). ¹³C NMR (δ c, 125 MHz, CDCl₃): 177.1, 176.0 (CO), 52.0 (NHCHCO), 41.9 (CMe₂), 42.1, 41.3, 31.8, 31.5, 30.1, 29.6, 29.5 (x2), 29.3, 28.9, 27.9 (CH₂), 25.3, 25.2 (CH₃), 24.8, 22.6 (CH₂) and 14.1 (CH₃). m/z (C₂₀H₃₈N₂O₂Na): 361.28350 (calculated: 361.2831). melting point 51-52 °C. [α]_{25D} (c = 1, CHCl₃) +28.0; [α]_{25D} (c = 0.87, MeOH) +13.3.

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66. Single Step



73%

Overview

Steps/Stages

Notes

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 2 h, rt

1) reaction from p.23 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

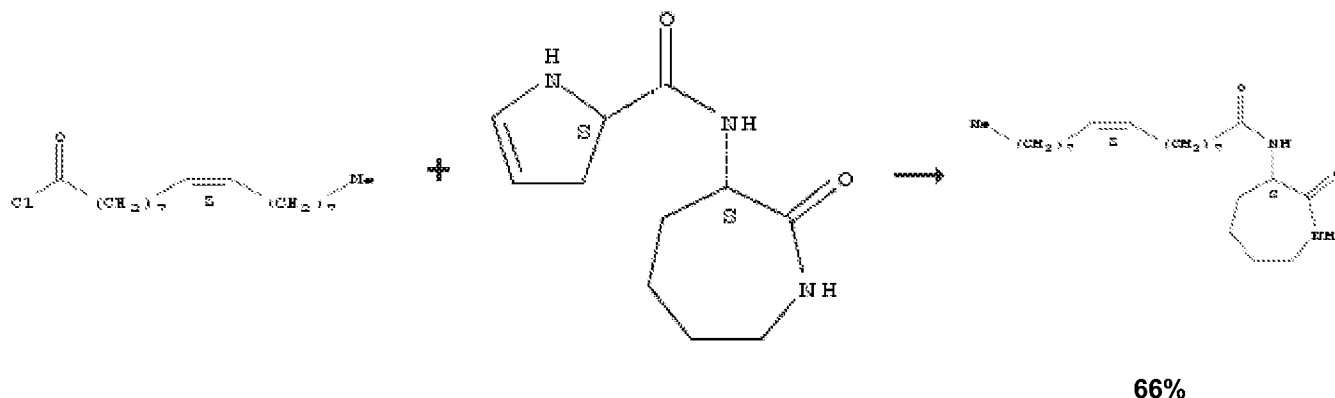
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 11: (R)-(Z)-3-(octadec-9-enoyl)amino-caprolactam:(R,R)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na₂CO₃ (6 mmol) in water (25 ml) were added to a solution of (Z)-octadec-9-enoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacuo. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (574 mg; 73%). (R)-(Z)-3-(octadec-9-enoyl)amino-caprolactam: Yield (574 mg; 73%). Melting point: 66-67 °C. [α]_{25D} (c=1, CHCl₃) = -31.4.

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67. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 2 h, rt

Notes

1) reaction from p.22 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

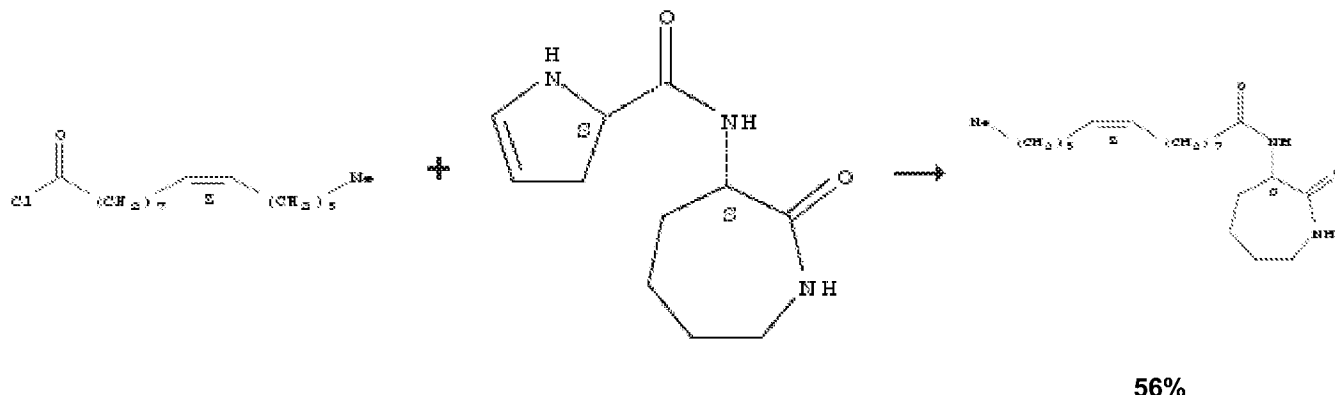
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 10: (S)-(Z)-3-(octadec-9-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na₂CO₃ (6 mmol) in water (25 ml) were added to a solution of (Z)-octadec-9-enoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacua. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (514 mg; 66%). (S)-(Z)-3-(octadec-9-enoyl)amino-caprolactam, Yield (514 mg; 66%). Melting point: 66-67 °C. [α]_D²⁵ (c = 1, CHCl₃) = +30.9. IR: ν_{max} (cm⁻¹): 3327, 3268 (NH), 1655, 1631 (CO), 1523 (NH). ¹H NMR (δ H, 500 MHz, CDCl₃): 6.88 (1H, d, J 5.5, CHNH), 6.74 (1H, br t, J 5, CH₂NH), 5.33-5.24 (2H, m, CH=CH), 4.49 (1H, ddd, J 11, 6, 1.5, CHNH), 3.29-3.14 (2H, m, CH₂NH), 2.16 (2H, t, J 7.5, CH₂CONH), 2.03 (1H, br d, J 13.5, ring CH), 1.99-1.89 (5H, m, ring CH + CH₂CH=CHCH₂), 1.84-1.72 (2H, m, ring CH), 1.58 (2H, br gn J 7.0, CH₂CH₂CONH), 1.42 (1H, br qd, J 14, 3, ring CH), 1.38-1.30 (1H, br m, ring CH), 1.30-1.14 (20H, m, (CH₂)₆CH₂CH=CHCH₂(CH₂)₄) and 0.83 (3H, t, J 7, CH₃). ¹³C NMR (δ C, 125 MHz, CDCl₃): 175.9, 172.3 (CO), 129.9, 129.7 (CH=CH), 52.0 (NHCHCO), 42.0 (NCH₂), 36.6, 31.8, 31.7, 29.7 (x2), 29.5, 29.3 (x3), 29.2, 29.1, 28.8, 27.9, 27.2, 27.1, 25.6, 22.6 (CH₂) and 14.1 (CH₃). m/z (C₂₄H₄₄N₂O₂Na): 415.32820 (calculated: 415.3300).

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68. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 2 h, rt

Notes

1) reaction from p.21 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

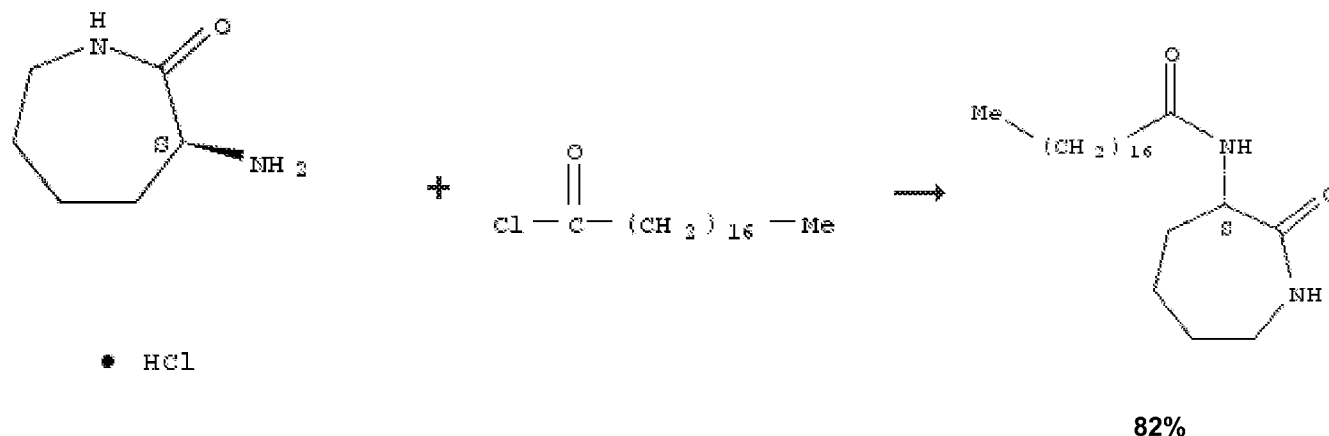
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 9: (S)-(Z)-3-(hexadec-9-enoyl)amino-caprolactam: (S,S)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (2 mmol) and Na₂CO₃ (6 mmol) in. water (25 ml) were added to a solution of (Z)-hexadec-9-enoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacuo. The residue was purified by silica column chromatography (eluent: EtOAc to 9:1 EtOAc:MeOH) to give the title compound (406 mg; 56%). (S)-(Z)-3-(hexadec-9-enoyl)amino-caprolactam, yield (406 mg; 56%) (S)-(Z)-3-(hexadec-9-enoyl)amino-caprolactam. Melting point: 67-68 °C. [α]_D²⁵ (c = 1, CHCl₃) = +33.2. IR: ν_{max} (cm⁻¹): 3324, 3268 (NH), 1655, 1630 (CO), 1524 (NH). ¹H NMR (δ H, 500 MHz, CDCl₃): 6.88 (1H, d, J 5.5, CHNH), 6.67 (1H, br s, CH₂NH), 5.33-5.25 (2H, m, CH=CH), 4.50 (1H, ddd, J 11, 6, 1, CHNH), 3.29-3.16 (2H, m, CH₂NH), 2.17 (2H, t, J 7.5, CH₂CONH), 2.03 (1H, br d, J 13, ring CH), 1.99-1.90 (5H, m, ring CH + CH₂CH=CHCH₂), 1.84-1.72 (2H, m, ring CH), 1.58 (2H, br qn J 7.0, CH₂CH₂CONH), 1.43 (1H, br qd, J 14, 3, ring CH), 1.38-1.30 (1H, br m, ring CH), 1.30-1.14 (16H, m, (CH₂)₄CH₂CH=CHCH₂(CH₂)₄) and 0.84 (3H, t, J 7, CH₃)- ¹³C NMR (δ C, 125 MHz, CDCl₃): 175.9, 172.3 (CO), 129.8 (x2) (CH=CH), 52.0 (NHCHCO), 42.0 (NCH₂), 36.6, 31.7 (x2), 29.7 (x2), 29.2 (x2), 29.1, 29.0, 28.8, 27.9, 27.2, 27.1, 25.6, 22.6 (CH₂) and 14.1 (CH₃)- m/z (C₂₂H₄₀N₂O₂Na): 387.29700 (calculated: 387.2987).

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69. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 2 h, rt

Notes

1) regioselective, reaction from p.20 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

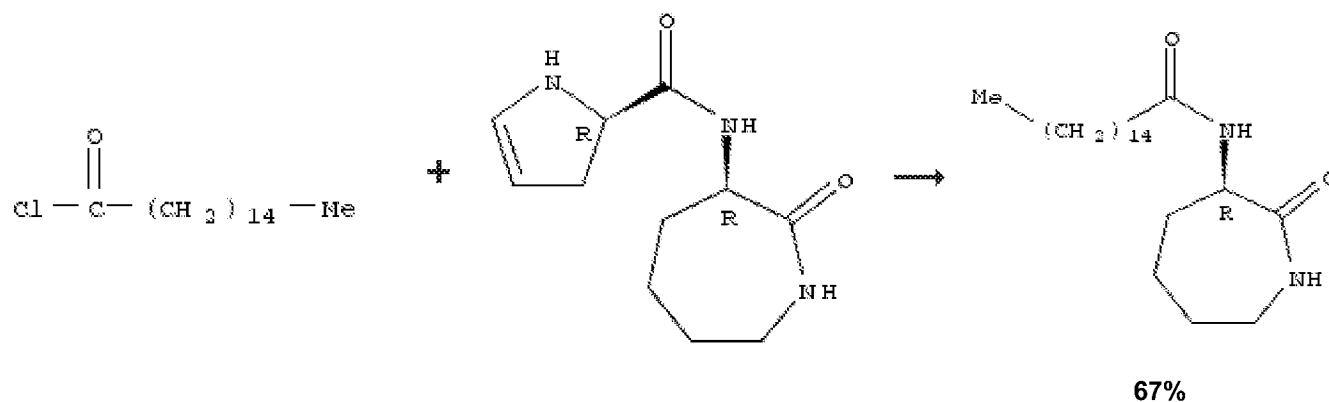
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 8: (S)-3-octadecanoylamino-caprolactam: (S)-3-amino-caprolactam hydrochloride (2 mmol) and Na₂CO₃ (6 mmol) in water (25 ml) were added to a solution of octadecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacuo. The residue was purified by recrystallisation from EtOAc to give the title compound (648 mg; 82%). (S)-3-octadecanoylamino-caprolactam: Yield (648 mg; 82%). Melting point: 87-88 °C. [α]_{25D} (c = 1, CHCl₃) = +31.9. IR: ν_{max} (cm⁻¹): 3327, 3272 (NH), 1667, 1655, 1631 (CO), 1524 (NH). ¹H NMR (δ H, 500 MHz, CDCl₃): 6.88 (1H, d, J 5.5, CHNH), 6.72-6.58 (1H, br m, CH₂NH), 4.50 (1H, dd, J 11, 6, CHNH), 3.29-3.16 (2H, m, CH₂NH), 2.17 (2H, t, J 7.5, CH₂CONH), 2.03 (1H, br d, J 13, ring CH), 1.99-1.90 (1H, m, ring CH), 1.86-1.73 (2H, m, ring CH), 1.58 (2H, br qn J 7.0, CH₂CH₂CONH), 1.42 (1H, br qd, J 14, 3, ring CH), 1.38-1.30 (1H, br m, ring CH), 1.30-1.14 (28H, m, (CH₂)₄) and 0.84 (3H, t, J 6.5, CH₃). ¹³C NMR (δ c, 125 MHz, CDCl₃): 175.9, 172.3 (CO), 52.0 (NHCHCO), 42.1 (NCH₂), 36.6, 31.9, 31.7, 29.6 (x8), 29.4, 29.3 (x2), 29.2, 28.8, 27.9, 25.6, 22.6 (CH₂) and 14.1 (CH₃)- m/z (C₂₄H₄₆N₂O₂Na): 417.34460 (calculated: 417.3457).

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70. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 2 h, rt

Notes

1) reaction from p.20 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

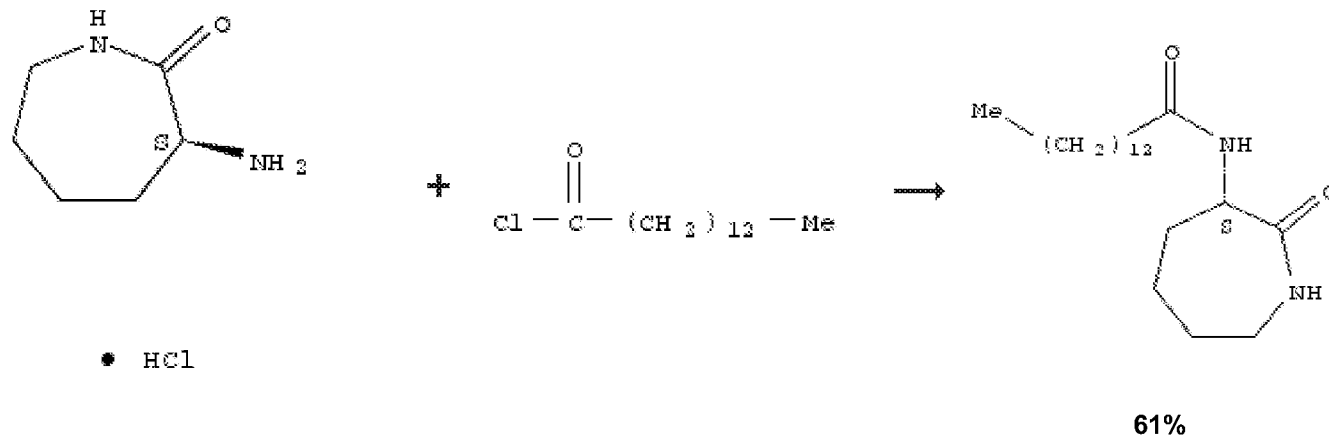
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005063702, 16 Jun 2005

Experimental Procedure

Example 7: (R)-3-hexadecanoylamino-caprolactam: (R,R)-3-amino-caprolactam hydro-pyrrolidine-5-carboxylate (5 mmol) and Na₂CO₃ (15 mmol) in water (25 ml) were added to a solution of hexadecanoyl chloride (5 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacuo. The residue was purified by recrystallisation from EtOAc to give the title compound (1.23 g; 67%). (R)-3-hexadecanoylamino-caprolactam, Yield (1.23 g; 67%). Melting point: 99-100 °C. [α]_{25D} (c=1, CHCl₃) = -32.0.

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71. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 2 h, rt

Notes

1) regioselective, reaction from p.19 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents

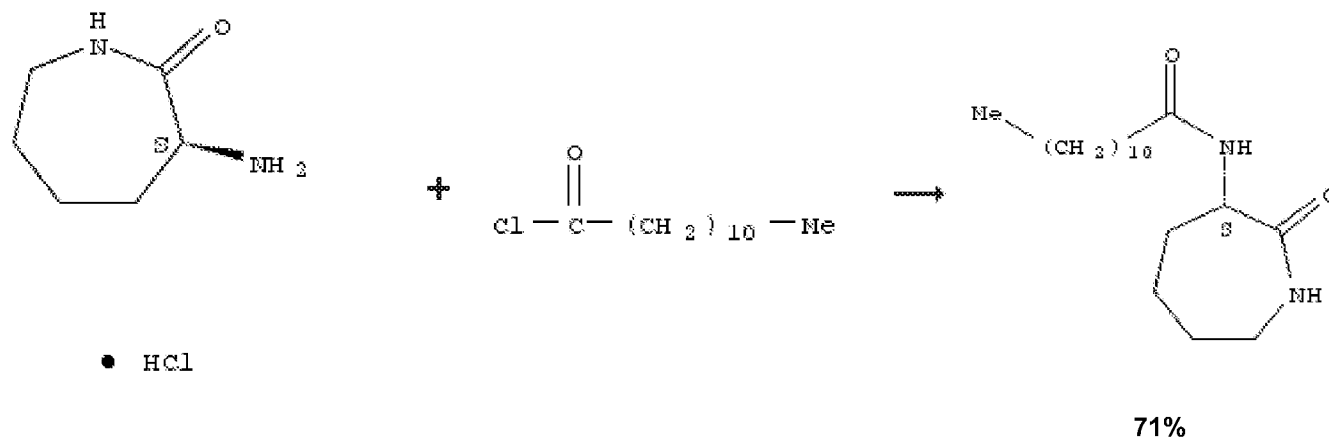
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 6: (S)-3-tetradecanoylamino-caprolactam: (S)-3-amino-caprolactam hydrochloride (2 mmol) and Na₂CO₃ (6 mmol) in water (25 ml) were added to a solution of tetradecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacuo. The residue was purified by recrystallisation from EtOAc to give the title compound (412 mg; 61%). (S)-3-tetradecanoylamino-caprolactam, Yield (412 mg; 61%). Melting point: 97-98 °C. [α]_D²⁵ (c=1, CHCl₃) = +33.2. IR: ν_{max} (cm⁻¹): 3326, 3273 (NH), 1666, 1655, 1631 (CO), 1523 (NH). ¹H NMR (δ H, 500 MHz, CDCl₃): 6.87 (1H, d, J 5.5, CHNH), 6.66-6.48 (1H, br m, CH₂NH), 4.50 (1H, dd, J 11, 6, CHNH), 3.30-3.16 (2H, m, CH₂NH), 2.18 (2H, t, J 7.5, CH₂CONH), 2.04 (1H, br d, J 13.5, ring CH), 2.00-1.92 (1H, m, ring CH), 1.86-1.74 (2H, m, ring CH), 1.59 (2H, br qn J 7.0, CH₂CH₂CONH), 1.43 (1H, br q, J 12.5, ring CH), 1.31 (1H, br q, J 13, ring CH), 1.31-1.13 (20H, m, (CH₂)₁₀) and 0.85 (3H, t, J 6.5, CH₃). ¹³C NMR (δ c, 125 MHz, CDCl₃): 175.9, 172.3 (CO), 52.0 (NHCHCO), 42.1 (NCH₂), 36.6, 31.9, 31.7, 29.6 (x4), 29.4, 29.3 (x2), 29.2, 28.8, 27.9, 25.6, 22.6 (CH₂) and 14.1 (CH₃), m/z (C₂₀H₃₅N₂O₂Na): 361.28270 (calculated: 361.2831).

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72. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 2 h, rt

Notes

1) reaction from p.19 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

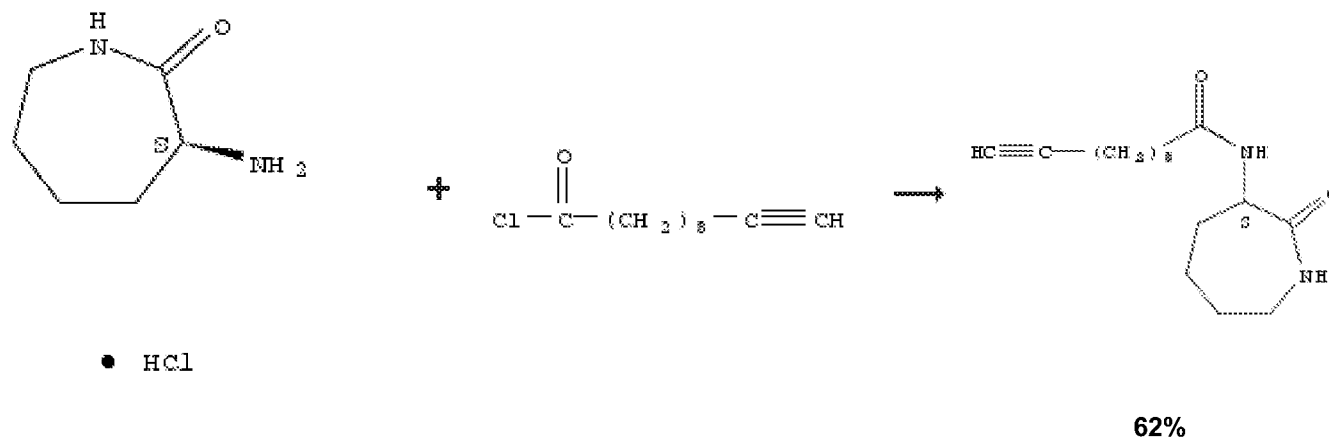
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 5: (S)-3-dodecanoylamino-caprolactam: (S)-3-amino-caprolactam hydrochloride (2 mmol) and Na₂CO₃ (6 mmol) in water (25 ml) were added to a solution of dodecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacua. The residue was purified by recrystallisation from EtOAc to give the title compound (439 mg, 71%). (S)-3-dodecanoylamino-caprolactam, Yield (439 mg, 71%). Melting point: 93-94 °C. [α]_D²⁵ (c=1, CHCl₃) = +35.5. IR: ν_{max} (cm⁻¹): 3324, 3267 (NH), 1666, 1630 (CO), 1521 (NH). ¹H NMR (δ H, 500 MHz, d₆-DMSO): 7.76 (1H, br s, CH₂NH), 7.67 (1H, d, J 7, CHNH), 4.38 (1H, dd, J10.5, 7.5, CHNH), 3.15 (1H, ddd, J15.5, 11.5, 5, CHHNH), 3.05 (1H, dt, J 14.5, 5.5, CHHNH), 2.17-2.07 (2H, m, CH₂CONH), 1.90- 1.80 (1H, m, C-5 H), 1.77-1.68 (2H, m, C-4 H, C-6 H), 1.62 (1H, br qt, J 12, 3.5, C-5 H), 1.46 (2H, br qn J 6.0, CH₂CH₂CONH), 1.36 (1H, qd, J 12.5, 2.5, C-4 H), 1.31-1.13 (17H, m, (CH₂)₈ + C-6 H) and 0.85 (3H, t, J 6.5, CH₃). ¹³C NMR (δ c, 125 MHz, d₆-DMSO): 174.4 (CO-ring), 171.2 (CO-chain), 51.3 (NHCHCO), 40.7 (NCH₂), 35.3, 31.4, 31.3, 29.1 (x3), 29.0 (x2), 28.8, 28.7, 27.8, 25.4, 22.2 (CH₂) and 14.0 (CH₃). m/z (C₁₈H₃₄N₂O₂Na): 333.25150 (calculated: 333.2518).

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73. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 2 h, rt

Notes

1) reaction from p.18 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

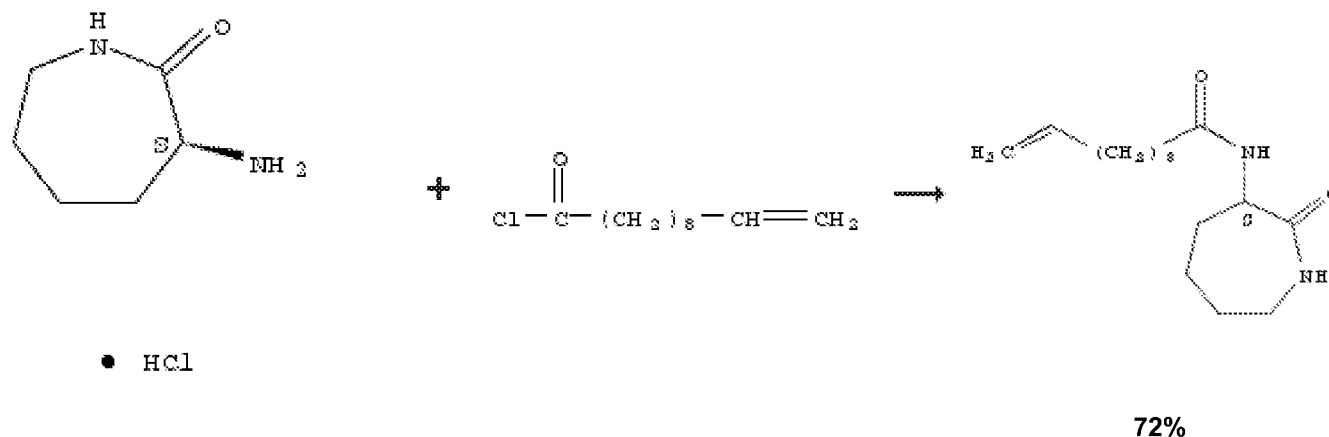
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 4: (S)-3-(undec-10-ynoyl)amino-caprolactam: (S)-3-amino-caprolactam hydrochloride (2 mmol) and Na₂CO₃ (6 mmol) in water (25 ml) were added to a solution of undec-10-ynoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacua. The residue was purified by recrystallisation from EtOAc to give the title compound (362 mg; 62%). (S)-3-(undec-10-ynoyl)amino-caprolactam, Yield (362 mg; 62%). Melting point: 73-75 °C. [α]_D²⁵ (c=1, CHCl₃) = +42.1. IR: ν_{max} (cm⁻¹): 3332, 3295 (NH), 1667, 1633 (CO), 1523 (NH). ¹H NMR (δ H, 500 MHz, d₆-DMSO): 7.76 (1H, t, 75.5, CH₂NH), 7.68 (1H, d, 77, CHNH), 4.36 (1H, dd, J₁₁, 7, CHNH), 3.16 (1H, ddd, J_{15.5}, 11.5, 5, CHHNH), 3.03 (1H, br dt, J₁₄, 7, CHHNH), 2.17-2.07 (4H, m, CH₂CONH + CH₂CCH), 1.85 (1H, m, C-5 H), 1.77-1.67 (2H, m, C-4 H, C-6 H), 1.62 (1H, br qt, J₁₃, 3.0, C-5 H), 1.50-1.28 (5H, m, CH₂CH₂CONH + HCCCH₂CH₂ + C-4 H) and 1.28-1.13 (9H, m, (CH₂)₄ + C-6 H). ¹³C NMR (δ c, 125 MHz, d₆-DMSO): 174.4 (CO-ring), 171.3 (CO-chain), 84.6 (CH₂CCH), 71.1 (CH₂CCH), 51.3 (NHCHCO), 40.7 (NCH₂), 35.2, 31.3, 29.0, 28.8, 28.7, 28.5, 28.2, 28.0, 27.8, 25.4 and 17.8 (CH₂). m/z (C₁₇H₂₈N₂O₂Na): 317.20470 (calculated: 315.2048).

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74. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 2 h, rt

Notes

1) reaction from p.17 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

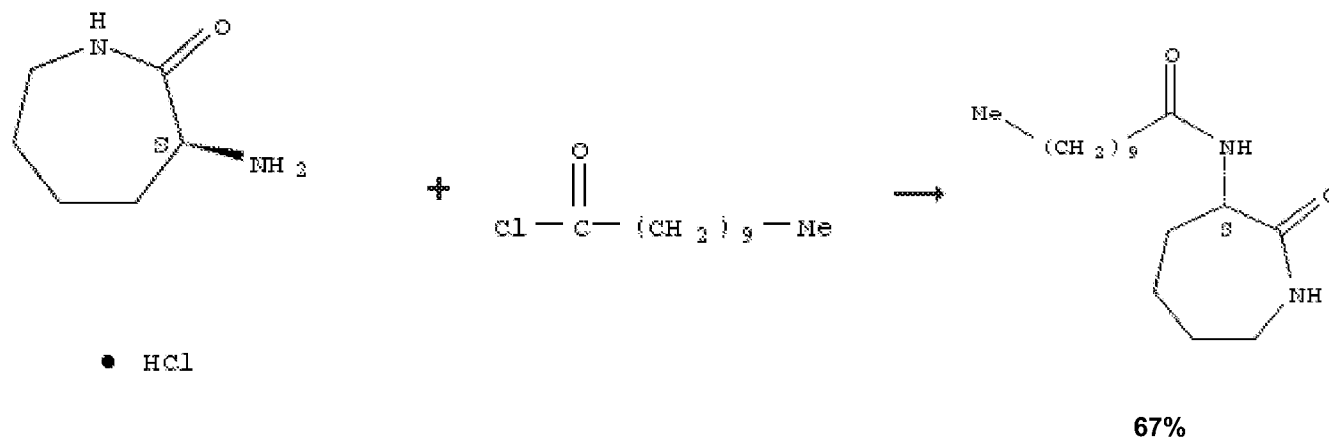
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 3: (S)-3-(undec-10-enoyl)amino-caprolactam: (S)-3-amino-caprolactam hydrochloride (2 mmol) and Na₂CO₃ (6 mmol) in water (25 ml) were added to a solution of undec-10-enoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacuo. The residue was purified by recrystallisation from EtOAc to give the title compound (423 mg; 72%). (S)-3-(undec-10-enoyl)amino-caprolactam, Yield (423 mg; 72%). Melting point: 83-84 °C. [α]_D²⁵ (c=1, CHCl₃) = +40.1. IR: ν_{max} (cm⁻¹): 3327, 3273 (NH), 1655, 1630 (CO), 1521 (NH). ¹H NMR (δ H, 500 MHz, d₆-DMSO): 7.75 (1H, t, J₆, CH₂NH), 7.66 (1H, d, J₇, CHNH), 5.76 (1H, ddt, J₁₇, 10, 6.5 CH₂=CH), 4.96 (1H, dq, J₁₇, 2, CHH=CH), 4.96 (1H, ddt, J₁₇, 2, 1, CHH=CH), 4.36 (1H, dd, J₁₀, 7, CHNH), 3.14 (1H, ddd, J_{15.5}, 11.5, 5, CHHNNH), 3.03 (1H, br dt, J₁₃, 5.5, CHHNNH), 2.16-2.06 (2H, m, CH₂CONH), 1.98 (2H, br q, J₇, CH₂=CHCH₂), 1.85 (1H, dt, J_{10.5}, 3, C-5 H), 1.75-1.67 (2H, m, C-4 H, C-6 H), 1.60 (1H, qt, J₁₃, 3.5, C-5 H), 1.44 (2H, br qn, J₇, CH₂CH₂CONH), 1.39-1.27 (3H, m, CH₂=CHCH₂CH₂ + C-4 H) and 1.31-1.13 (9H, m, (CH₂)₄ + C-6 H). ¹³C NMR (δ C, 125 MHz, d₆-DMSO): 174.4 (CO-ring), 171.3 (CO-chain), 138.9 (CH₂=CH), 114.7 (CH₂=CH), 51.3 (NHCHCO), 40.7 (NCH₂), 35.3, 33.3, 31.3, 29.0, 28.9 (x2) 28.7, 28.6, 28.4, 27.8 and 25.4 (CH₂)- m/z (C₁₇H₃₀N₂O₂Na): 317.21970 (calculated: 317.2205).

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75. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 2 h, rt

Notes

1) reaction from p.17 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

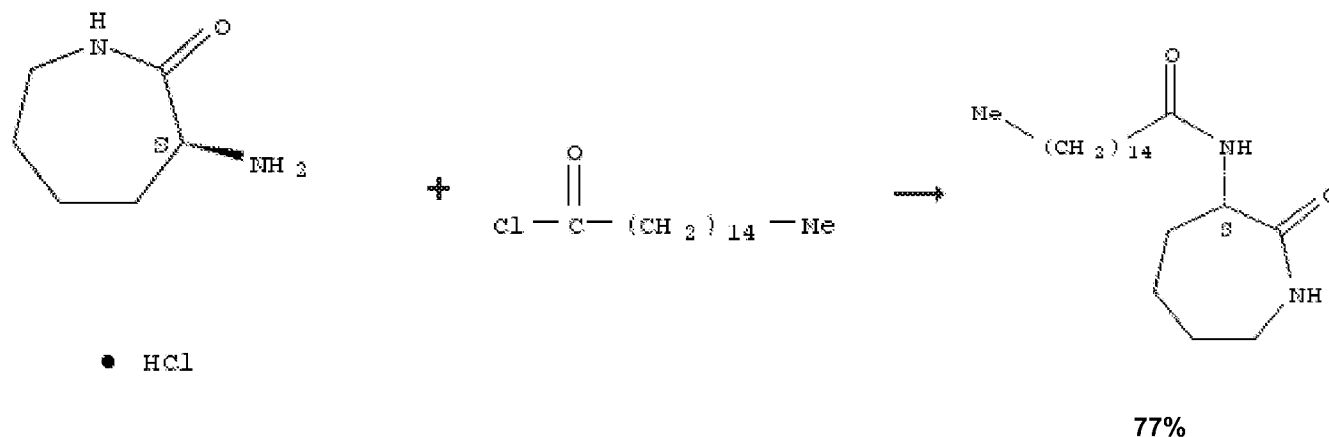
Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 2: (S)-3-undecanoylamino-caprolactam: (S)-3-amino-caprolactam hydrochloride (2 mmol) and Na₂CO₃ (6 mmol) in water (25 ml) were added to a solution of undecanoyl chloride (2 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacuo. The residue was purified by recrystallisation from EtOAc to give the title compound (397 mg, 67%). (S)-3-undecanoylamino-caprolactam, Yield (397 mg, 67%). Melting point: 91-92 °C. [α]_D²⁵ (c = 1, CHCl₃) = +30.2. 1R: ν_{max} (cm⁻¹): 3342, 3313 (NH), 1676, 1638 (CO), 1519 (NH); 3342, 3292 (NH), 1671, 1639 (CO), 1513 (NH). 1H NMR (δ H, 500 MHz, d₆-DMSO): 7.76 (1H, t, J 6, CH₂NH), 7.68 (1H, d, J 7, CHNH), 4.38 (1H, dd, J 10, 7, CHNH), 3.15 (1H, ddd, J 15.5, 11, 5, CHHNH), 3.04 (1H, dt, J 13, 6, CHHNH), 2.19-2.06 (2H, m, CH₂CONH), 1.85 (1H, dt, J 10.5, 3, C-5 H), 1.77-1.68 (2H, m, C-4 H, C-6 H), 1.60 (1H, qt, J 12, 3.5, C-5 H), 1.46 (2H, br gn J 6.5, CH₂CH₂CONH), 1.35 (1H, qd, J 12.5, 3, C-4 H), 1.31-1.13 (15H, m, (CH₂)₇ + C-6 H) and 0.85 (3H, t, J 7.0, CH₃). 13C NMR (δ c, 125 MHz, d₆-DMSO): 174.4 (CO-ring), 171.3 (CO-chain), 51.3 (NHCHCO), 40.7 (NCH₂), 35.2, 31.4, 31.3, 29.1, 29.0 (x2), 28.9, 28.8, 28.7, 27.8, 25.4, 22.2 (CH₂) and 14.0 (CH₃)- m/z (C₁₇H₃₂N₂O₂Na): 319.23540 (calculated: 319.2361).

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76. Single Step



Overview

Steps/Stages

1.1 R:Disodiumcarbonate, S:H₂O, S:CH₂Cl₂, 2 h, rt

Notes

1) reaction from p.16 in patent, Reactants: 2, Reagents: 1, Solvents: 2, Steps: 1, Stages: 1, Most stages in any one step: 1

References

Preparation of 3-aminocaprolactam derivatives as anti-inflammatory agents
By Grainger, David John, Fox, David John
From PCT Int. Appl., 2005053702, 16 Jun 2005

Experimental Procedure

Example 1: (S)-3-hexadecanoylamino-caprolactam: (S)-3-amino-caprolactam hydrochloride (5 mmol) and Na₂CO₃ (15 mmol) in water (25 ml) were added to a solution of hexadecanoyl chloride (5 mmol) in dichloromethane (25 ml) at ambient temperature and the reaction mixture was stirred for 2 hours. The organic layer was then separated and the aqueous phase was extracted with additional dichloromethane (2 x 25 ml). The combined organic layers were dried over Na₂CO₃ and reduced in vacuo. The residue was purified by recrystallisation from EtOAc to give the title compound (1.41 g; 77%). (S)-3-hexadecanoylamino-caprolactam, Yield (1.41 g; 77%). Melting point: 99-100 °C. [α]_D²⁵ (c=1, CHCl₃) = +32.0. IR: ν_{max} (cm⁻¹): 3325, 3272 (NH), 1666, 1655, 1631 (CO), 1524 (NH). ¹H NMR (δ H, 500 MHz, CDCl₃): 6.88 (1H, d, J 5.5, CHNH), 6.72 (1H, br s, CH₂NH), 4.49 (1H, ddd, J 11, 6, 1, CHNH), 3.29-3.16 (2H, m, CH₂NH), 2.17 (2H, t, J 7.5, CH₂CONH), 2.03 (1H, br d, 7.13.5, ring CH), 1.98-1.89 (1H, m, ring CH), 1.85-1.73 (2H, m, ring CH), 1.58 (2H, br qn J 7.0, CH₂CH₂CONH), 1.43 (1H, br qd, J 14, 3, ring CH), 1.38-1.29 (1H, br m, ring CH), 1.29-1.14 (24H, m, (CH₂)₁₂) and 0.83 (3H, t, 7.6.5, CH₃). ¹³C NMR (δ C 125 MHz, CDCl₃): 175.9, 172.3 (CO), 52.0 (NHCHCO), 42.1 (NCH₂), 36.6, 31.9, 31.7, 29.6 (x6), 29.4, 29.3 (x2), 29.2, 28.8, 27.9, 25.6, 22.6 (CH₂) and 14.1 (CH₃). m/z (C₂₂H₄₂N₂O₂Na): 389.31450 (calculated: 389.3144).